

Ethnic differences in gestational diabetes identified by universal screening in routine antenatal care

A cross-sectional study

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Master thesis
Institute of Health and Society
Faculty of Medicine

UNIVERSITY OF OSLO

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Abstract

Background: Gestational diabetes mellitus (GDM) is defined as diabetes occurring or first recognized during pregnancy, and increases the risk of complications for both mother and the child during pregnancy, childbirth and beyond. Early detection is essential to prevent adverse outcomes associated with the condition and to reduce the increased risk of future diabetes type 2 in the women as well as the offspring. The STORK Groruddalen research program reported high prevalence of GDM in a multiethnic population of women attending Child Health Clinics (CHC) for antenatal care in Groruddalen, and large differences among the ethnic groups were observed. The current study aims to estimate the prevalence of GDM based on universal screening, which recently has been integrated as a part of the routine antenatal care in the same city districts, and to identify important risk factors for GDM.

Methods: For the diagnosis of GDM, all women attending the CHC's for routine care were invited to a 75 g oral glucose tolerance test between 24-34 weeks' of gestation after an overnight fast. Venous plasma glucose was measured on site, and GDM was diagnosed using the World Health Organization criteria from 1999. BMI, body fat and vitamin D level were also measured, and questionnaire data on age, parity, family history of diabetes etc. were obtained. Multiple logistic regression analyses were performed to examine associations between GDM and potential risk factors.

Results: The study sample consisted of 966 pregnant women (77% of invited), of whom 64% had ethnic minority background. Overall, 13.7% were found to have GDM, and there were large ethnic differences. The women from South Asia had the highest prevalence of 20.3%, followed by Middle East with 19.0%, both of which were significantly higher ($p=0.001$) than Western Europeans who were found to have a prevalence of 8.2%. Further, ethnic origin from South Asia and Middle East, first-degree relatives with diabetes, lower height and higher percentage body fat are risk factors associated with increased GDM risk.

Conclusion: The prevalence of GDM found in these districts in Groruddalen is high and varies with ethnic origin. Potential risk factors could help identify women with higher risk.

Sammendrag

Bakgrunn: Svangerskapsdiabetes, definert som diabetes som oppstår eller først oppdages i svangerskapet, øker risikoen for uønskede komplikasjoner for både mor og barnet under svangerskapet, fødselen og senere i livet. Tidlig identifisering er svært viktig for å kunne redusere assosierte negative utfall samt den forhøyde risikoen for kvinnen og barnet til å utvikle diabetes type 2 i fremtiden. Forskningsprogrammet STORK Groruddalen fant høy forekomst av svangerskapsdiabetes blant kvinner som besøkte helsestasjonene i bydelene i Groruddalen, og store forskjeller ble observert mellom de etniske gruppene. Disse bydelene tilbyr nå screening av svangerskapsdiabetes som en integrert del av svangerskapsomsorgen. Hensikten med denne studien er å undersøke prevalensen samt identifisere risikofaktorer for svangerskapsdiabetes i de samme bydelene etter innføringen av dette nye tjenestetilbudet.

Metode: Alle gravide kvinner som kom til helsestasjonen mellom svangerskapsuke 24 og 34, ble tilbudt en 2-timers 75 g glukosebelastning. Fastende og 2-timers verdi ble målt fra venøst blod, og svangerskapsdiabetes diagnostisert etter Verdens Helseorganisasjons kriterier fra 1999. Videre ble BMI, fettprosent og vitamin D nivå målt, og det ble registrert opplysninger om blant annet alder, paritet og diabetes i familien. Logistisk regresjonsanalyser ble utført for å undersøke assosiasjoner mellom svangerskapsdiabetes og potensielle risiko faktorer.

Resultater: Utvalget bestod av 966 gravide kvinner (77% av de inviterte), hvorav 64% hadde etnisk minoritetsbakgrunn. Av disse var det totalt 13.7% som hadde svangerskapsdiabetes, og prevalensen varierte sterkt med etnisk bakgrunn. Kvinner fra Sør-Asia hadde den høyeste prevalensen på 20.3%, etterfulgt av kvinner fra Midtøsten med 19.0%. Begge hadde statistisk signifikant høyere prevalens enn Norge med 8.2% ($p=0.001$). Videre var etnisk bakgrunn fra Sør Asia og Midtøsten, samt høyere fettprosent, lav høyde og diabetes i familien assosiert med høyere risiko for svangerskapsdiabetes.

Konklusjon: Funnene i studien tyder på en høy forekomst av svangerskapsdiabetes i disse bydelene i Groruddalen, og prevalensen varierer sterkt med etnisk bakgrunn. Potensielle risikofaktorer kan identifisere kvinner med høyere risiko.

Preface

This thesis is written as a part of a two-year master program in Health Sciences, Institute of health and society, University of Oslo. My interest in minority health emerged a couple of years ago while studying public health nutrition, and I am very grateful for the opportunity to continue to explore this important field of research as part of this master thesis. Although challenging at times, the whole process of writing this paper has been truly rewarding with a personal learning curve that has reached a considerable level.

First I would like to express my sincere gratitude to my supervisor, Anne Karen Jenum, leader of the STORK Groruddalen research program and associate professor at the University of Oslo and Oslo and Akershus University College of Applied Sciences. She has been available for me at all times, considered my questions thoughtfully and always shown great interest. This thesis has also benefited from discussions with Professor Nina Vøllestad, co-supervisor of the work. I want to thank her for pinpointing details and sharing her thoughts on parts of this thesis.

My special thanks go to all staff at the Child Health Clinics in Stovner, Grorud and Bjerke, who have been responsible for the data collection and provided me with these data. In addition, they have been very helpful during the whole process and always responded to my requests for additional information or clarifying.

Finally, I would like to thank my family for the patience, continuous support and believing in me.

Fjerdingby, May 2014

Anam Shakil

Abbreviations

CHC	Child Health Clinics
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
HAPO Study	Hyperglycemia and Adverse Pregnancy Outcome Study
IADPSG	The International Association of the Diabetes and Pregnancy Study Group
NDDG	National Diabetes Data Group
OGTT	Oral Glucose Tolerance Test
PG	Plasma Glucose
REC	Regional Committees for Medical and Health Research Ethics
STORK	STORK Groruddalen study
T2DM	Type 2 diabetes mellitus
US	United States of America
WHO	World Health Organization

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1 Introduction

The burden of chronic diseases such as obesity and type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide (Darnton-Hill, Nishida, & James, 2004). Changes in diets and lifestyles resulting from industrialization, urbanization and economic development have accelerated during the last decades and have significant impact on the health status of populations all around the world. Improved standards of living consisting of easy access to energy-dense foods along with a decline in the demands of physical activity both lead to negative consequences in terms of inappropriate dietary patterns and a more sedentary lifestyle (Nishida, Shetty, & Uauy, 2004). These trends are worrying not only because such conditions affect a large proportion of the population, but also because they have started to appear earlier in life (Darnton-Hill et al., 2004).

Along with the rising tide of the current global epidemic of diabetes, an increase in gestational diabetes mellitus (GDM) is also observed (Ferrara, 2007). GDM is defined as diabetes occurring or first recognized during pregnancy, and is especially of concern as it increases the risk of complications for both mother and the child during pregnancy, childbirth and beyond (Buckley et al., 2012). Around 50% of women with GDM are expected to develop T2DM within 5 years after delivery (Kim, Newton, & Knopp, 2002). Their offspring are also at increased risk of developing obesity, impaired glucose tolerance, and diabetes as children or young adults, compared to those not exposed to maternal diabetes during fetal life (Ferrara, 2007).

In Norway, as well as in the rest of Europe, the number of immigrants from Asia, Africa and South America has been rapidly increasing. As per 1 January 2014, the foreign-born population accounted for 14.9% of the total population in Norway. In some Eastern parts of Oslo, such as Groruddalen, immigrants from non-Western countries have reached >44% of the whole population (Statistics Norway, 2014). This part of Oslo has since long been perceived as an area with low socioeconomic status, and shown to have markedly lower work participation rates, mean income as well as education, and the rates of people on social benefits are higher in Groruddalen compared to most other districts of Oslo (Thorsnæs & Gundersen, 2008). There are also marked differences in health between those on top and those on the bottom of the social hierarchy, and as in the rest of Europe, the social gap in Norway is not decreasing (Jenum, Stensvold, & Thelle, 2001; Marmot et al., 2012).

Several immigrant groups are shown to have higher prevalence of poor health outcomes than the majority of the population, including musculoskeletal problems, vitamin D deficiency, anemia, and stomach cancer (Abebe, 2010; Hjern, 2012). Ethnic differences are also observed in the prevalence of obesity, T2DM and GDM (Hedderson, Darbinian, & Ferrara, 2010). In Europe, a high prevalence of diabetes has repeatedly been found in South Asians (Bhopal et al., 1999) Caribbean's and other groups with ancestral origin from Africa (Davey Smith, Chaturvedi, Harding, Nazroo, & Williams, 2000) as well as in people with Middle Eastern, Turkish and Moroccan origin (Uitewaal, Manna, Bruijnzeels, Hoes, & Thomas, 2004). This indicates that ethnic minorities are disproportionately more affected by T2DM and GDM than the host population. In Groruddalen, Jenum, Holme, Graff-Iversen, and Birkeland (2005) found an alarmingly high prevalence of diabetes, especially in South Asian women (27.5% versus 2.9% in Norwegians). They also found that the majority of middle-aged non-Western women were physically inactive and obese. In addition, migrant populations have been shown to have a higher prevalence of T2DM compared to the prevalence in their native countries (A. Misra & Ganda, 2007; Zargar et al., 2004), indicating that environmental factors may have an important role (Hedderson et al., 2010).

The growing segment of the Norwegian population represented by recent immigrants may influence the proportion of women diagnosed with GDM and ultimately type 2 diabetes. This is a critical public health concern as GDM might reflect or contribute to the current patterns of increasing diabetes and obesity (Ferrara, 2007). Coordinated efforts along with additional resources are required by the health care system to provide care during pregnancy and to reduce adverse perinatal outcomes. Increased knowledge regarding the epidemiology of this condition is important as it may lead to new approaches to alter the trends in GDM and to prevent chronic diabetes in women and their offspring.

1.1 STORK Groruddalen

In light of this growing public health concern and as a response to the “National strategy to reduce social inequalities in health” launched in 2007, a research program was initiated in 2008 in which pregnant women and their offspring were targeted. Its main purpose was to increase the knowledge about GDM in a multiethnic population and establish better methods for identification of high-risk pregnancies. To this end, it was carried out in the residential areas of Groruddalen, Oslo, and the study program was given the name STORK Groruddalen (STORK). The ultimate

goal of this population-based cohort study was to reduce complications and long-term health risks for the mother and the offspring, and to develop and implement health promotion strategies related to care during pregnancy and infancy at the local level (Jenum et al., 2010).

Women were recruited at the Child Health Clinics (CHC) in three chosen administrative city districts: Bjerke, Grorud and Stovner. In total, 823 pregnant women attending the CHC's for antenatal care were included, and data from questionnaires, physical examinations, urine samples, vitamin D, oral glucose tolerance test (OGTT) and much more were collected during three visits (Jenum et al., 2010). Paternal questionnaire data were also collected. Two of the visits were during pregnancy, and one visit was three months post-partum. The women were tested for GDM at 28 weeks of gestation, e.g. the second visit.

The study found a surprisingly high prevalence of GDM; 13.0% overall, with large differences among the ethnic groups (Jenum et al., 2012). As a result of the high prevalence rates reported, the three CHC's continued to offer screening for GDM as a part of the antenatal routine program after the study completion. The measurement of the women's vitamin D status was also continued, as the majority of women (80%) from the ethnic minority groups were vitamin D-deficient (Jenum, 2010). The Norwegian Directorate of Health contributed and partly funded the strengthened antenatal care in these districts.

Universal screening with an OGTT as part of the standard routine care is, as far as we know, offered only at these CHC's (Bjerke, Grorud and Stover), in Groruddalen, as the current national guidelines recommend selective screening based on risk factors (Directorate for Health and Social Affairs, 2009). This is the first time in Norway all pregnant women are given equal possibility to be identified with GDM by being routinely tested in the antenatal care.

The high rates of this disorder found in the STORK Groruddalen study have been questioned, making it especially important to validate these findings in another larger sample. Additionally, it has led to a strengthening of the antenatal care in these districts, with implications such as increased local workload and health care costs. It is therefore an urgent need to compare prevalence rates reported with results from a new study from routine care, with the goal to ensure that such structural changes are necessary and beneficial.

The present study aims to determine the ethnic differences in the prevalence of GDM assessed as

part of the routine at the CHC's. The screening is optional; however, most women choose to perform it according to the CHC staff. Moreover, more women are likely to participate as screening is offered as a routine. This will allow for a better representativeness and potential selection bias occurring in STORK-Groruddalen could be reduced. The current study opens a unique window to explore prevalence rates and risk factors outside a research setting. Furthermore, a high prevalence of GDM may indicate a need to implement universal screening in the antenatal care in Norway.

The next chapter of this thesis will present the aims and the theoretical background of the study. Chapter 4 describes the methods applied, the data collection process as well as the statistical analyses. Next, the results will be presented and discussed in light of previous research in the field. The last chapter is a conclusion and summary of the main findings in this study.

2 Aims & Research questions

Main objective

- Measure and compare the prevalence rates and risk factors of GDM in different ethnic groups

Secondary objective

- Compare the prevalence rates in this study from routine care with results from STORK-Goruddalen collected in a research setting

The main research questions are:

What is the prevalence of women with GDM in the largest ethnic minority groups compared to Western Europeans?

What are the risk factors found to be associated with GDM?

3 Background

3.1 Gestational diabetes mellitus

3.1.1 The definition

Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset, or first recognition during pregnancy (Buchanan, Xiang, Kjos, & Watanabe, 2007; Metzger et al., 2007). The definition acknowledges the possibility that patients may have undiagnosed diabetes prior to the pregnancy, or hyperglycemia induced by the pregnancy. Usually the blood glucose levels normalize and symptoms subside after birth, but this is not a prerequisite in the definition (Landon & Gabbe, 2011).

3.1.2 Metabolic adaptations during normal pregnancy and GDM

Throughout a normal pregnancy, a series of complex metabolic changes occur to ensure an adequate and continuous supply of nutrients to the growing fetus (Butte, 2000). The pregnancy state can be viewed as a diabetogenic and inflammatory state in which the glucose and lipid metabolism are altered resulting in higher levels of maternal fat deposition, hyperlipidemia and insulin resistance (Bilhartz, Bilhartz, Bilhartz, & Bilhartz, 2011).

Insulin, which is a hormone produced by pancreatic β -cells, enables the cells to increase the glucose uptake from blood, and use it as fuel or convert it to glycogen in liver and muscles. Insulin resistance is a decreased biological response to a given concentration of insulin at the target tissue, e.g. liver, muscle or adipose tissue (Catalano, 2010). In pregnancy, the resistance to insulin, beginning near mid-pregnancy and progressing through the third semester (Buchanan & Xiang, 2005) increases about 50-60% (Catalano, 2010). This may result from a combination of increased maternal adiposity and hormones secreted by the placenta. In healthy women, the pancreatic β -cells increase their insulin secretion as a response to the pregnancy induced insulin resistance in order to keep blood glucose levels in the normal range. In other words, the balance between insulin resistance and insulin supply is maintained, resulting in rather small changes in circulating glucose levels over the course of pregnancy compared with the large changes in insulin sensitivity (Buchanan et al., 2007).

In the pathophysiology of GDM, inadequate insulin secretion to compensate for the insulin resistance is caused by pancreatic β -cell dysfunction and plays a central role (Metzger et al., 2007). To maintain stable blood glucose levels over the course of pregnancy, robust plasticity of β -cell function is necessary (Buchanan et al., 2007). Many underlying causes of such a β -cell dysfunction have been suggested, however, a chronic insulin resistance represents the majority of cases (Buchanan, Xiang, & Page, 2012). Women who develop GDM are thought to have a reduced capacity to adapt to the increased insulin resistance, leading to maternal hyperglycemia.

3.1.3 Adverse outcomes

The presence of GDM has important consequences and increases the risk of complications for both mother and child during pregnancy, childbirth and beyond (Buckley et al., 2012). Lesser degrees of glucose intolerance have also been shown to be harmful (Yogev et al., 2010), and the immediate and long-term clinical sequelae are significant contributors to the burden of disease in many countries (Jiwani et al., 2012). The following section will describe adverse maternal and fetal outcomes associated with GDM.

3.1.3.1 Offspring

Excessive fetal growth remains an important perinatal concern in GDM. The placenta is the primary interface between the mother and her child. As maternal glucose can freely pass the placenta, increased glucose concentrations on the maternal side will result in increased glucose fluxes from mother to fetus (Metzger et al., 2007). Compensating for the excessive glucose transfer, the fetus has to increase the secretion of insulin to the same extent, leading to fetal hyperinsulinemia. This might in turn lead to increased growth and adiposity, as insulin is a growth hormone (Pedersen, 1971). Macrosomia, characterized by disproportionately increased fetal growth, occur more frequently in infants of women with GDM than their healthy counterparts.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was conducted to clarify unanswered questions on the association between maternal glycaemia and the risk of adverse pregnancy outcomes. This large study, carried out in 15 centers in nine countries, showed that there was a continuous relationship between maternal blood glucose levels following a 75g glucose load (fasting, 1-hour and 2-hours) and the primary outcomes; above 90-percentile for birth weight and cord C-peptide, clinically neonatal hypoglycemia and caesarean section, and the secondary outcomes; preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia and

need for intensive neonatal care (Hapo Study Cooperative Research Group et al., 2008).

Numerous studies are consistent with the results from the HAPO study, showing a relationship between higher maternal glucose and increasing frequency of adverse perinatal outcomes (Jensen et al., 2008; Pettitt, Knowler, Baird, & Bennett, 1980; Sermer et al., 1995).

There are also a number of studies relating maternal glycaemia to long-term consequences in the offspring (Pettitt & Knowler, 1998); however, these effects are less clear and well-described than the immediate effect on fetal growth. Consequences of a hyperglycemic or hyper-nutritional uterine environment are suggested include an increased vulnerability to develop obesity and diabetes in adult life (Dabelea & Crume, 2011; Kelstrup et al., 2013). A recent analysis of the HAPO study, however, did not find a relationship between maternal glucose levels and child obesity at 2 years age (Pettitt et al., 2010).

3.1.3.2 Maternal

The majority of women with GDM will return to normal glucose tolerance immediately after delivery; however, a significant number will remain diabetic or continue to have impaired glucose tolerance (Metzger et al., 2007). GDM can therefore be considered an early marker of disturbances in the glucose metabolism, and more than a disease (Buchanan et al., 2012), can be viewed as a risk factor for type 2-diabetes (Landon & Gabbe, 2011). Women with a previous GDM history are shown to have a 7-fold risk of future type 2 diabetes, compared with their normal non-diabetic counterparts (Bellamy, Casas, Hingorani, & Williams, 2009). It is estimated that about 10% of the women with GDM develop type 2 diabetes within four years, and up to 60% ten years postpartum (Buchanan et al., 2012).

The HAPO study (Hapo Study Cooperative Research Group et al., 2008) suggested a relationship between maternal glycaemia and preeclampsia, which is defined as hypertension and proteinuria that develops during pregnancy (Bilhartz et al., 2011). Also, as women with a history of GDM have been found to have higher values of markers of endothelial dysfunction, as well as increased intimal medial thickness of the carotid arteries compared to healthy women (Bo et al., 2007), GDM has been recognized as a risk factor for future cardiovascular disease (Bilhartz et al., 2011; Kessous, Shoham-Vardi, Pariente, Sherf, & Sheiner, 2013).

Fetal macrosomia is in addition associated with increased risk of difficult delivery and maternal damage, and this is confirmed in large populations (Boulet, Alexander, Salihu, & Pass, 2003;

Esakoff, Cheng, Sparks, & Caughey, 2009). Furthermore, the consequences of excessive fetal growth include birth trauma and maternal morbidity from operative delivery. The cesarean delivery rate is also increased in patients with GDM, in part to avoid birth trauma (Metzger et al., 2007).

3.1.4 Diagnostic criteria

It has been proposed a large number of procedures and glucose cut-off values for the diagnosis of glucose intolerance in pregnancy over the time (World Health Organization [WHO], 2013). The first GDM criteria were established in the 1960's by O'Sullivan and Mahan, who found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy (Buchanan & Xiang, 2005). By investigating the distribution of plasma glucose values of pregnant women, they proposed diagnostic criteria for gestational diabetes based on a 3-h 100 g OGTT. Later they validated these criteria against the development of future diabetes in the mother (WHO, 2013). GDM was diagnosed if two or more blood glucose values were ≥ 2 standard deviations above the population mean.

In the 1980's, the National Diabetes Data Group (NDDG) adapted these cut-off points to newer methods for measuring glucose due to advanced laboratory techniques, and applied them to the definition of gestational diabetes (Buchanan & Xiang, 2005). The American Diabetes Association and many other associations accepted the NDDG recommendation and these criteria, with modifications, remain in use today, mainly in the US. The World Health Organization's recommendation from 1999 is based on a 2-h 75g OGTT and applies the same diagnostic criteria for GDM as for diabetes and impaired glucose tolerance for non-pregnant adults. These criteria are used in Norway along with other European and developing countries. None of these diagnostic criteria are directly based on perinatal outcomes, and rather focus on the women's risk of developing diabetes after pregnancy (Paglia & Coustan, 2011).

The International Association of the Diabetes and Pregnancy Study Group (IADPSG) was formed in 1998 to facilitate an international approach to enhancing the scientific understanding, diagnosis and management of diabetes in pregnancy (International Association of et al., 2010). Recently, the multinational HAPO study demonstrated a continuum of risk for maternal glycaemia and adverse pregnancy outcomes (Hapo Study Cooperative Research Group et al., 2008), leading to the IADPSG proposing a new set of guidelines for GDM. This recommendation was based on the

fasting 2-h 75 g OGTT used in the HAPO study to standardize the glucose load internationally, and said that all women not previously diagnosed with diabetes should be evaluated at 24-28 weeks' of gestation. Specific cut-offs were set above which women would be diagnosed with GDM, reflecting an odds ratio [OR] of at least 1.75 for birth weight, cord C-peptide or percentage body fat greater than the 90th percentile, compared to neonates of women with glucose values below the mean (International Association of et al., 2010).

In light of new data and considering the fact that the diagnostic criteria from 1999 are over ten years old and not evidence-based, the WHO also updated their recommendations for hyperglycemia in pregnancy in 2013, endorsing the criteria proposed by IADPSG (WHO, 2013). These new criteria and the WHO 1990 criteria, which are still in use in Norway, are presented in table 1.

Table 1 Threshold values for diagnosis of GDM, with a 75-g glucose challenge. Values in mmol/l.

Definition	Fasting PG	1-h PG	2-h PG
WHO 1999	7.0		7.8
IADPSG/ WHO 2013	5.1	10.0	8.5

*** At least one of the venous plasma glucose (PG) values must be met or exceeded for the diagnosis of GDM.**

3.1.5 Screening

For the diagnosis of GDM, an OGTT, preferably between 24 and 28 weeks, is needed. Nevertheless, routine screening for GDM and the most effective approach for the systematic detection of this disorder remain controversial topics (Buckley et al., 2012). Different protocols are in use internationally and there are different recommendations regarding which pregnant women should be selected for biochemical testing, how the test should be performed and what glycaemic threshold should be considered diagnostic (Walker, 2008). Also, screening practices are inconsistent across Europe and even within countries. Some recommend systematic screening of all pregnant women while others test on a case- by-case basis according to established risk factors and clinician or patient decisions (Buckley et al., 2012).

The WHO and IADPSG both recommend the 75-g OGTT. IADPSG guidelines recommend screening all or high-risk women at the initial visit, whereas the WHO has not stated any guidance

as to which women should undergo the OGTT. In North America, screening has commonly involved a two-step approach for all women; a non-fasting 1-hour 50 g glucose challenge test at the first antenatal visit (Berger & Sermer, 2009; Vandorsten et al., 2013), and those with abnormal glucose values proceed to the second step, which is to undergo either a 100-g or a 75-g OGTT for the diagnosis of GDM (Buchanan et al., 2012).

In Norway, screening for GDM using risk factors is recommended in a healthy population. The Directorate for Health and Social Affairs (2009) recommended the 2-hour 75 g OGTT for women with: Morning glycosuria; Age > 38 years; First degree relatives with diabetes; BMI > 27 kg/m²; A history of GDM or an ethnic origin from a country outside Europe with high diabetes prevalence.

3.1.6 Prevalence

Estimating the prevalence of gestational diabetes is made difficult by a lack of universally accepted diagnostic criteria, as well as variation in screening procedures, differences in sample population and methodologies used (Reece, Leguizamon, & Wiznitzer, 2009). As a result, it has been difficult to compare the prevalence of GDM among ethnic groups or to determine whether GDM rates have changed over time (Buckley et al., 2012).

The reported prevalence of GDM varies from 1 to 20%, and ethnic differences in the prevalence most certainly exist (Buckley et al., 2012; Jiwani et al., 2012; Lamberg, Raitanen, Rissanen, & Luoto, 2012; Schneider, Bock, Wetzel, Maul, & Loerbroks, 2012). In the US, Asians, Hispanics and African-American women have been reported to be at a higher risk of GDM than non-Hispanic white women (Ferrara, Hedderson, Quesenberry, & Selby, 2002; Ferrara, Kahn, Quesenberry, Riley, & Hedderson, 2004; Thorpe et al., 2005). Similarly, a study from Australia showed higher prevalence among women born in China or India compared to women whose country of birth was in Europe or Northern Africa (Beischer, Oats, Henry, Sheedy, & Walstab, 1991). Likewise in Europe, GDM is found to be more common among Asian women than Europeans (Dornhorst et al., 1992). Noteworthy, the proportion of women with GDM is lower in Asian countries when compared to the proportion observed in Asian women living in other continents (Yang et al., 2002). In India, it was observed that GDM was more common in women living in urban areas than in women living in rural areas (Zargar et al., 2004). A large study reviewing European evidence relating to the prevalence of GDM reported a trend where lower

prevalence in Northern or Atlantic seaboard part of Europe predominates, while higher estimates have been detected in the South and Mediterranean seaboard regions (Buckley et al., 2012).

In Norway, the prevalence of GDM in the total population is not documented, however, a few studies report a rate of 6-7% among selected groups of ethnic Norwegian women (Frosli et al., 2013; Voldner et al., 2008). The STORK Groruddalen study recently reported an overall prevalence of 13.0% (with the 1999 WHO-criteria) where several ethnic groups, such as South Asians and Middle Easterners, were found to have a higher prevalence (14.8 and 16.9%, respectively) compared with Western Europeans (10.8%) (Jenum et al., 2012).

The rate of GDM is rising worldwide in line with increasing trends of maternal obesity and type 2 diabetes (Finucane et al., 2011; Wijesuriya, Williams, & Yajnik, 2010). Moreover, the prevalence of GDM usually reflects the underlying prevalence of type 2 diabetes in the population studied (Ferrara, 2007; Moses & Cheung, 2009). Middle East and South Asia are found to have the highest increase in the prevalence of diabetes (Chan et al., 2009), and rates are higher for ethnic minority groups living in western countries compared with the host population (Hu, 2011; Jenum et al., 2005; Wandell, Carlsson, & Steiner, 2010).

3.1.7 Risk factors

As GDM and T2DM share pathophysiological similarities (Barbour et al., 2007; Buchanan et al., 2012) and have the same genetic susceptibility, risk factors similarities also exist between the two disorders (Ben-Haroush, Yogeve, & Hod, 2004). Several risk factors for gestational diabetes mellitus are well known and discussed in the literature. Among these are advanced maternal age, obesity, prior GDM history and family history of diabetes (Dode & dos Santos, 2009). For other risk factors, such as parity, race or ethnicity, physical activity and socioeconomic factors, some inconsistency between studies exists. It is highly significant to identify these risk factors, in particular the modifiable ones, to be able to prevent GDM among high-risk populations.

Among the well-recognized modifiable risk factors, excessive adiposity is the most commonly investigated with consistent findings (Chu et al., 2007). Obesity induces insulin resistance and chronic B-cell dysfunction (Buchanan et al., 2007), and a meta-analysis concluded that the risk for GDM increases substantially and progressively in overweight, obese and morbidly obese women

(Chu et al., 2007). It is, however, important to note that the majority of obese subjects maintain normal glucose tolerance (Abdul-Ghani, Lyssenko, Tuomi, DeFronzo, & Groop, 2009).

Available data suggest that health behaviors like dietary habits and physical activity influence the development of GDM (Oostdam, van Poppel, Wouters, & van Mechelen, 2011; Zhang & Ning, 2011). Some studies indicate that physical activity right before and during pregnancy could modify the risk (Dode & dos Santos, 2009). Epidemiologic studies on the role of dietary factors for GDM are at their early stage, and even though a low glycaemic index diet might be beneficial, conclusions cannot be drawn regarding diet (Oostdam et al., 2011; Zhang & Ning, 2011).

It has been observed that some racial and ethnic groups have higher frequencies of GDM, leading to a number of studies evaluating the role of racial factors (Dode & dos Santos, 2009). Ethnicity may be defined as the social group a person belongs to, which implies shared culture, history, geographical origins, language, diet, physical, genetic and other factors (Bhopal, 2004). Being member of an ethnic group with high prevalence of diabetes, generally including Hispanic, Native American, South and East Asian, black Caribbean and those of Pacific Islands ancestry and Middle Eastern descent (American Diabetes, 2012; Hedderston et al., 2010) is suggested as a risk factor.

Dode and dos Santos (2009) noted that high prevalence of GDM was found among ethnic groups in studies carried out with populations of immigrants in Western countries. However, the prevalence is lower in studies made in the original countries of these populations. This indicates that factors associated to the immigrant situation or to socioeconomic conditions might play a role. In the US and other countries as well, most ethnic minorities are more likely to be poorer and less educated than the white population. It has therefore been discussed whether the high prevalence of diabetes is attributable to ethnicity or if it is due to socioeconomic status (Link & McKinlay, 2009).

Socioeconomic position (SEP), referring to the socially derived economic factors that influence what position individuals or groups hold within the multiple-stratified structure of a society (Galobardes, Lynch, & Smith, 2007; Krieger, Williams, & Moss, 1997), is shown to influence health outcomes over the life course. Poorer socioeconomic circumstances may lead to poorer health by operating through several complex mechanisms like stress and underuse of health services, resulting in an unequal distribution of some conditions across socioeconomic groups

(Brown et al., 2004; Galobardes et al., 2007; D. P. Misra & Grason, 2006). For instance, subjects with poor SEP are reported to have inadequate health behavior, and a higher risk for T2DM (Agardh, Allebeck, Hallqvist, Moradi, & Sidorchuk, 2011; Evenson & Wen, 2010; Stringhini et al., 2012). Likewise, an inverse association between GDM and socioeconomic level has been found in some studies, where level of education in particular is inversely associated with GDM after adjustment for other socioeconomic and demographic variables (Innes et al., 2002). Nevertheless, the association between SEP and GDM has not been comprehensively studied and it is not clear if socioeconomic level can be viewed as a risk factor (Anna, van der Ploeg, Cheung, Huxley, & Bauman, 2008; Cullinan et al., 2012; Dode & dos Santos, 2009).

Increasing observational and experimental evidence show that growth and development during fetal and early life have an important role for health later in life (Gluckman, Hanson, Cooper, & Thornburg, 2008; Godfrey, 1998; Lehen, Zechner, & Haaf, 2013). Mother's diet, body composition and health determine the intrauterine environment (Hanson & Gluckman, 2011), in which the human fetus is growing and able to adapt. If the adaptation is permanent, it is considered as a "programming" change with persistent effects in structure, function and metabolism (Wadhwa, Buss, Entringer, & Swanson, 2009). Some of these offspring programmed to survive undernutrition continue to be malnourished and stunted during childhood. The programming is often beneficial in the short run, and as long as they have the same lifestyle as in the early life, they remain at a relatively low risk for non-communicable diseases later in life (Veeraswamy, Vijayam, Gupta, & Kapur, 2012). However, it might be detrimental if there is a "mismatch" between the offspring's predicted living environment and actual living environment (Hanson & Gluckman, 2011), which can be changed by migrating to urban areas as adult and lead to changes in the macro environment for which they were not programmed (Ramachandran et al., 2004; Snehalatha & Ramachandran, 2009). Such changes in life circumstances increase the risk for adverse health outcomes, and subjects that grow up in affluent societies are found to be at higher risk of hypertension, T2DM and cardiovascular disease at much lower birth weight, BMI and central adiposity threshold (Pilgaard et al., 2010). These effects may in young women present first during pregnancy, resulting in GDM (Seshiah, Balaji, Balaji, Paneerselvam, & Kapur, 2009). Several studies report associations between GDM and low birth weight, as well as GDM and short adult stature (stunting) (Ogonowski & Miazgowski, 2010).

3.1.8 Treatment and effect

A number of studies indicate that early detection and management of GDM improves outcomes for both mother and child (Crowther et al., 2005; Landon et al., 2009; Reece et al., 2009; Sacks, 2009). Initial treatment is aimed at lowering blood glucose concentrations and involves changes in diet, moderate exercise and glucose self-monitoring. The majority of women will benefit from antenatal management of GDM consisting of such lifestyle modifications (Falavigna et al., 2012; Petry, 2010). However, these figures depend on the population studied, methods applied and content of the intervention (Falavigna et al., 2012). There are several options available for intensifying therapy beyond lifestyle modifications as well. When dietary management does not achieve desired glucose control, insulin and oral antidiabetic medications may be used (Hartling et al., 2013).

Two large randomized controlled trials have shown significant reduction in perinatal complications with these strategies, compared to women with GDM receiving routine prenatal care alone (Crowther et al., 2005; Landon et al., 2009). These studies found that treatment results in lower incidence of macrosomia, large-for-gestational-age, shoulder dystocia and preeclampsia in pregnancy. However, the effect on childhood obesity was less convincing even though there were fewer “big babies” at birth (Gillman et al., 2010; Pettitt et al., 2010). Moreover, current research does not show a treatment effect of GDM on future poor metabolic outcomes of the offspring (Hartling et al., 2013).

4 Material and methods

Systematic observation and testing can be accomplished using a wide variety of methods, however, two general approaches are widely recognized: qualitative research or quantitative research. The selection of scientific method depends primarily on the research questions being asked and the type of data being collected (Johannessen, Tufte, & Kristoffersen, 2010). Aliga and Gundersen (as cited in Muijs, 2011, p. 1) describe quantitative research as: "...Explaining phenomena by collecting numerical data that are analyzed using mathematically based methods (in particular statistics)". By contrast, qualitative research is a subjective approach used to describe life experiences and give them meaning, and is not usually numerical (Johannessen et al., 2010). For this study a quantitative approach is found to be most appropriate and its selection is based upon the problem of interest e.g. assessing the prevalence rates of a condition, which requires data being collected in numerical form.

4.1 Study design

A cross-sectional study aims at determining the frequency of a particular attribute, such as a disease, specific health outcomes or any other health-related event, in a given population at a particular point in time (Levin, 2006). Data can be collected on individual characteristics, including exposure to risk factors, alongside information about the outcome.

This study entails the collection of data on a cross-section of the population, comprising a proportion of it, e.g. all women attending the Child Health Clinics in Groruddalen, Oslo, for antenatal care. It is descriptive in nature, providing a prevalence rate at a particular point in time, as well as assessing the factors providing the outcome (Frigessi, Moger, Scheel, Skovlund, & Veierod, 2006). Moreover, the study can be considered population-based, implying sampling of individuals from a geographically defined general population (Szklo, 1998).

Prevalence and incidence are two closely related terms, and both estimates are reported in the literature regarding GDM, often used interchangeably (Golden et al., 2012). In this study, prevalence, defined as the proportion of a population found to have a condition at a given point in time, is chosen over incidence, which is a measure of new cases arising in the study population during a defined period of time (Rothman, 2012). According to Mosdol and Brunner (2005) prevalence is often used to estimate the disease burden in a population, for instance to plan health

services. As GDM is assessed at a given point in time in a woman's pregnancy, the term prevalence was found to be most appropriate.

4.2 Setting

The study invited all women attending the Child Health Clinics in Groruddalen, Oslo (Stovner, Grorud, and Bjerke administrative city districts) for antenatal care. These districts cover a population of 87,257 and reflect diverse ethnical backgrounds. The proportion with ethnic minority origin in Stovner, Grorud and Bjerke was 42.8%, 36.0% and 29.7%, respectively, in 2014 (Statistics Norway, 2014).

Antenatal care is a routine part of pregnancy, provided free of cost to all women living in the districts to monitor the mother and baby's health. This care can be delivered in primary, secondary or community setting, and the women have the option of visiting midwives at the CHC'S, the general practitioner (GP) or a combination of both. For healthy normal women, a schedule of eight routine appointments is regarded adequate, offered from the first trimester up to gestational week 40. Ultrasound examination is also performed in one of these appointments to determine the date of term, usually around 17-20 weeks' of gestation.

The CHC's in Stovner, Bjerke and Grorud offer one additional antenatal appointment at gestational week 28± for screening. Patients are screened for GDM by undergoing a 2-h 75 g oral glucose tolerance test. When receiving the standard information about the antenatal care, all women are given information about this test and requested to come in the fasting state. Information letters developed in the STORK Groruddalen study program, available in 8 different languages, are used for this purpose. Furthermore, patients are informed about STORK Groruddalen and the high prevalence of GDM found for all ethnic groups in the study. The benefits of screening are highlighted as well as the fact that results will be known to the women immediately after the test. Information based on routinely recorded data from these appointments, collected and provided by staff at these CHC'S, will be presented in the following chapters.

4.3 Study population

The population of interest for a particular study question is called the population at risk or the target population (Mosdøl & Brunner, 2005). In this study, all pregnant women living in these districts constitute the target population. The data collection period lasted from March 2011 to

December 2012; however, Bjerke city district started the screening a year after the other two so that the inclusion period lasted for one year only (2012) for this CHC. According to data monitoring the activity at the CHC's, mainly based on the number of newborns in the districts, it is estimated that approximately 70-80% attend the CHC's during their pregnancy.

During the inclusion period, a total of 1561 pregnant women visited the three CHC's for antenatal care. The numbers of invited, included and excluded subjects are presented in a flowchart (figure 1). A number of women were not offered the screening either because of attendance at the CHC late in their pregnancy or due to logistic and administrative challenges at the CHC's (holidays, sick leave etc.). Of those invited, some choose to perform screening at their GP's or have already undergone it, while a few did not wish to be tested. Other reasons include moving out of the area or not being able to make it to the scheduled appointment due to holidays etc. Our best estimate based on routine monitoring data and information from the staff at the CHC's indicates that 1313 subjects were eligible and invited. As 1018 women accepted the invitation to perform screening we have estimated that at least 77% of the eligible women accepted the invitation to be screened for GDM.

Further, to be included in the analyses of this study, the OGTT had to be performed between 24 and 34 weeks' of gestation, unless diagnosed with GDM at an earlier point in the pregnancy, as some women (n=4) were tested earlier due to known risk for GDM before 24 weeks' (GDM in previous pregnancies etc.). The main reason for exclusion was gestational week e.g. too early or late attendance (n=26).

Other reasons for being excluded were not being able to complete the OGTT due to hyperemesis and difficulties drinking the glucose mix. Women experiencing vomiting before one hour after drinking the glucose were excluded due to presumably invalid test results (n=16), while cases of vomiting occurring after one hour have been included (n=8). Some had problems drawing blood and were excluded for this reason (n=2). Five women were not tested as they did not meet fasting, and two were unable to perform the OGTT due to hyperemesis. Three women were not given glucose because of high fasting plasma glucose (FPG) and referred to their GP instead. Their fasting values have been included but the 2-h values are missing. The study sample consists of 966 women, constituting 95% of those who accepted the invitation for screening with OGTT.

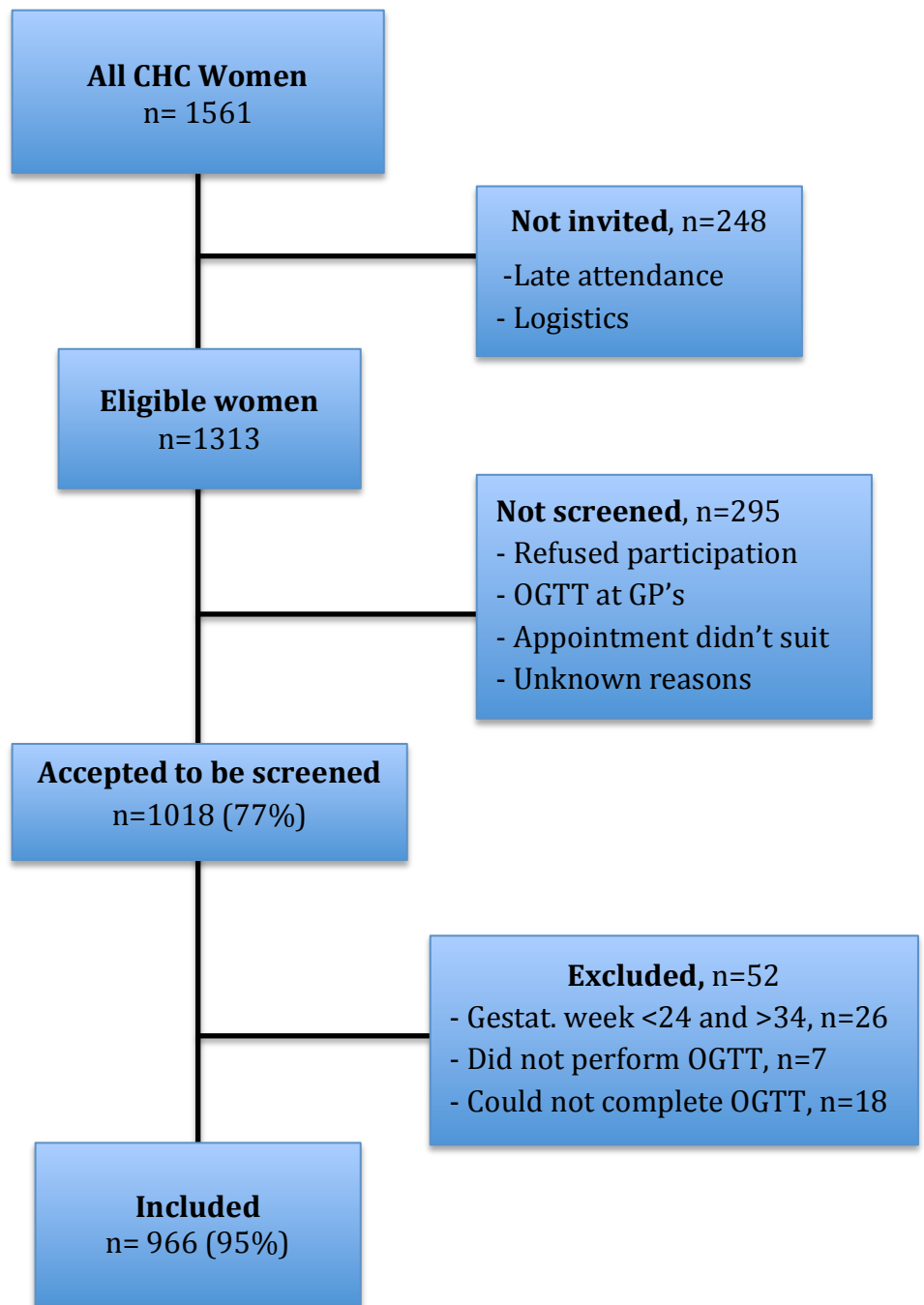


Figure 1 Attendance at the CHC from March 2011 to December 2012; those eligible, those who were not offered screening, those not screened and those who were excluded in this study by reasons for exclusion.

4.4 Data collection

Data collection was entirely performed by the CHC staff. However, data was registered from the questionnaires by me, for which EpiData Entry was used - a software designed for simple or programmed data entry and data documentation.

4.4.1 Description of the background variables

A questionnaire is a written instrument used to obtain information from study subjects (World Health Organization, 2008). Demographic and historical information were obtained by trained midwives, using a standardized interviewer-administrated questionnaire (appendix 1). In contrast to a self-administered approach where questionnaires are answered at by the respondents themselves (ibid.), the women in this study provided answers to the midwife who noted them on the questionnaire. The following is a description of the background information that the women were asked to self-report on.

4.4.1.1 Demographics

Age

Upon arrival at the CHC's, the date of the visit and the women's date of birth were registered. These variables were used to calculate the age, a continuous variable. Age was later divided into three categories for use in certain analysis. The cut points for the categories were selected to have approximately the same proportion of subject in each age group.

Ethnic origin

In this study, ethnic origin was defined by the participant's country of birth or the participant's mother's country of birth if she was born outside of Norway. Ethnic origin was self-reported by most women and was otherwise obtained from medical records. In cases where ethnic origin was lacking in both the questionnaires and medical records, the staffs at the CHC's were contacted directly to request this missing information.

The women's country of origin was further categorized into ethnic origin groups (regions) commonly used in medical research (Danaei et al., 2011) and as previously applied in the STORK Groruddalen study (Jenum et al., 2010) prior to analysis. The categories were as following: Norway & other Western (including North America), South Asia, Middle East (including North Africa/Central Asia), Sub-Saharan Africa (except North Africa), Eastern Europe, East Asia and South America (including Central America).

This variable was in addition recoded into "Norway & Other Western" and "Non-Western" (including all other groups), for one specific analysis to check for differences between the study

sample and excluded subjects. This was mainly done due to small sample size in most of the ethnic group in the excluded sample.

4.4.1.2 Obstetric and medical information

Gestational week at inclusion

Women are offered a routine ultrasound examination in a previous appointment (between gestational week 17-20) from which estimation of the woman's expected date of delivery is made. This date was noted on the questionnaire, and later used to determine the gestational age at OGTT. In case of missing expected date of delivery, the woman's date of last menstrual period was used for this purpose. The following formula has been used to determine the gestational age at point of OGTT:

$$\begin{aligned} \text{Expected date of delivery} - 282 &= \text{last date of menstrual period} \\ (\text{Date of visit} - \text{last date of menstrual period})/7 &= \text{gestational age in weeks} \end{aligned}$$

Parity

If the woman had been pregnant previously, the number of live births was reported. Parity was defined as the number of previous pregnancies lasting more than 22 weeks. This was originally a continuous variable, which was later reclassified into nulliparous (no previous pregnancy), uniparous (one previous pregnancy) and multiparous (two or more previous pregnancies) for the analysis.

Family history of diabetes

The woman was asked to report if she had any first-degree relatives with diabetes. Family history of diabetes was defined as a history of type 2 diabetes, type 1 diabetes or unknown diabetes type in any family members, including parents, siblings or children. This variable was recoded into having first-degree relatives with known diabetes and having relatives without known diabetes.

Previous history of GDM

All women were asked whether they have had GDM in previous pregnancies, and this information was registered as a dichotomous variable with the responds 'yes' and 'no'. This variable will be presented only for the uniparous and multiparous women (≥ 1 children).

4.4.2 Description of the physical measurements

After responding to a number of questions related to the risk for GDM, the women went through a series of measurements and tests. Screening for gestational diabetes consists of the steps described in the next chapters.

4.4.2.1 Blood samples

The blood samples performed at the appointment consist of a 2-h OGTT and vitamin D test.

Oral glucose tolerance test

The oral glucose tolerance test measures the body's ability to use sugar (glucose), and is currently the gold standard for a definite diagnosis of GDM (Olabi & Bhopal, 2009).

Venous blood samples are drawn after an overnight fast. The second blood sample will be collected 2 hours after drinking a sweet liquid containing a measured amount of glucose (75 grams). Blood glucose was analyzed on site, within 5 min after vein puncture, in venous EDTA blood according to a standardized protocol, using a patient-near method (HemoCue 201+, Angelholm, Sweden). This method is preferred to give immediate results to allow optimal patient information and necessary actions when GDM is diagnosed (Jenum et al., 2010). In addition, venous blood tests were transferred to gel glass and sent for further analysis to the Akershus University hospital. The three instruments were externally validated during STORK (Jenum, 2010), and calibrated for plasma and with the same batch number for cuvettes and controls (run weekly). These procedures were followed after STORK as well.

GDM was diagnosed according to the 1999 WHO-criteria (if one of two criteria was met: FPG ≥ 7 or 2-h PG ≥ 7.8 mmol/l), and the results of the blood tests were made known to the mothers immediately after. Women with fasting values above 7 mmol/l, and 2-hour values of 7.8-8.9 mmol/l were given lifestyle and dietary advice, along with written information on how to manage the condition. These leaflets were developed in STORK Groruddalen study program for distribution to women with GDM, and were available in 8 different languages. Furthermore, these patients were remitted to their general practitioner for follow-up.

Those with fasting glucose >7.0 mmol/l or 2-hour values ≥ 9 mmol/l were referred to secondary care for follow-up. Letters with the laboratory results were sent to their general practitioners in addition.

The results, both the local values and laboratory values, were recorded in the questionnaire forms. For the diagnosis of GDM, the on-site values have been used. However, the glucose values analyzed at the hospital laboratory were used in cases of missing on-site values (FPG, n=4; 2-h PG, n=13), or values were extracted from the medical records (n= 2).

The fasting and 2-h plasma glucose values, originally continuous variables, were categorized into a binary form (GDM and non-GDM) based on a defined cut-off level, e.g. 1999 WHO-criteria. This was the main outcome variable, in other words the disease or health-related variable being studied (Mosdol & Brunner, 2005).

Vitamin D level

A 25(OH)D test is a blood test to determine the level of 25-hydroxyvitamin D. The plasma concentration of vitamin D was analyzed from the same venous blood sample drawn for fasting glucose. Women with vitamin D values below predefined limits were advised to take supplements and letters were sent to the their GP's.

4.4.2.2 Anthropometric assessments

Anthropometry involves the physical measurement of some or several aspects of human body size, and is relatively quick, simple and cheap to perform (Bates, Nelson, & Stanley, 2005).

Height, weight, BMI and body fat

Body height was measured to the nearest 0.1 cm with a fixed stadiometer. Height may serve as a proxy measure for early life socioeconomic factors, and stunting can be a marker of the nutritional status or living conditions during fetal and/or early life (Jenum et al., 2005; Ogonowski & Miazgowski, 2010). This variable was used with this intention in the regression analysis.

Body weight and composition was measured with a Tanita-weight BC 418 MA body fat analyzer (Tanita Corp., Tokyo, Japan) in light clothing and without shoes. The values for body fat were available in kilograms (kg) and percent (%). A simpler version of this device is validated in pregnant women previously (Ueda et al., 2006).

Body mass index (BMI) is the most commonly used measure of undernutrition and overnutrition in adults, and the easiest anthropometric measure of fatness (Bates et al., 2005). Pregnancy BMI was calculated as the maternal weight (in kilograms) divided by the square of height (in meters).

This variable, originally continuous, was later divided into three categories for certain analysis. The cut points for the categories were selected according to the WHO cut-off.

In addition, recalled maternal pre-pregnancy weight was self-recorded to the nearest kilograms. However, this variable is not the primary focus of this study because of its inherent subjectivity and the absence of data for one city district. Pre-pregnant BMI was calculated as pre-pregnant weight/measured height².

4.5 Statistics

After registration in Epidata, the data file was opened in SPSS version 20 (SPSS, Chicago, IL), where all analyses were carried out. Descriptive analyses were performed to obtain a description of the characteristics of the sample. To show differences between various ethnic groups, one-way ANOVA was performed for normally distributed continuous variables, and Pearson's chi-square test for categorical variables. Mean and standard deviation (SD) are presented for continuous variables, in addition to median and interquartile ranges (IQR), and number and percentage are reported for categorical variables.

For the main outcome variable (GDM), the differences in prevalence were tested for each ethnic group with the reference group (Norway & other Western) using a Pearson's chi-square test. Independent sample t-test was performed to determine any differences in continuous variables (age, BMI) between the two groups of data (with GDM and without GDM), as well as the study cohort and the excluded subjects.

To compare the prevalence rates from this study with the rates found in the STORK Gnoruddalen study, a Z-test for proportions has been used. This calculator is used to check whether there is a statistically significant difference between the observed results for the two independent groups, at the 95% confidence level.

Logistic regression analyses were performed to identify the effect of ethnicity and other predictors on the categorical outcome of GDM. Prior to adding variables into the models, multicollinearity was checked for by requesting collinearity diagnostics, and variables were included and removed from the model accordingly. Additionally, Pearson correlations were performed to check high

intercorrelations among the predictor variables, and the highest correlation coefficient found was 0.20.

In model A ethnicity was added showing the effect of each ethnic group along with age and parity. Other predictive factors were added step-wise. In model B, BMI and first-degree relatives with diabetes were added. The final model, model C, included height, percentage body fat and gestational week, while BMI and parity were removed. Variables were retained in the model if they were significant in the presence of other covariates or were known to be biologically important (well-established risk factors). Nagelkerke R^2 shows the explained variance of the model. Statistical significance level was set to $P < 0.05$, and a 95% CI for the odds ratio (OR).

4.6 Ethics

Ethical considerations apply throughout and are integral components of the research process. This study entails personal health information, which, according to the Regional Committees for medical and health research ethics (REC) (2012) is defined as: “Confidential information in accordance with section 21 of the Healthcare Personnel Act and other information and assessments regarding health conditions or which is of significance to health conditions, which can be associated with an individual”.

When conducting research on human biological material or personal health information, consent is the primary regulation rule. Informed consent is defined as “The process of agreeing to take part in a study based on access to all relevant and easily digestible information about what participation means, in particular, in terms of harms and benefits” (Parahoo, 2006, p. 469). In the current study, data was collected by midwives on a routinely basis at the CHC’s, mainly for clinical use. The women attending for antenatal care were informed about the STORK Groruddalen study, of which the screening for GDM is a result. However, they have not been informed that their data will be analyzed as part of this master thesis. Hence, no written consent was signed prior to the study and the participants were not given the right to withdraw or restrict their data from analysis.

In cases where personal health information has already been obtained without requesting consent, dispensation from professional secrecy requirements is necessary (REC, 2012). Based on the

degree of sufficient justification provided, REC provides advice on whether permission to access the requested confidential patient information should be given or not.

For this study, REC for South Eastern Norway approved the study protocol with the no 415316. The personnel involved in the data collection and preparation were bound by an oath of confidentiality, as was I when receiving the data material. The data routinely collected were stored separately at the CHC's and kept locked after collection. After receiving the data for this master thesis, data was stored at the University of Oslo, Department of General Practice at the office by Ullevål Hospital, and access was only possible from this place. The data were made anonymous after registration in Epidata, and confidentiality is preserved. There are no disclosures of information that may identify individuals.

4.7 Funding

There are no requested sources of expenses associated with this study. The improvement and strengthening of the routine antenatal care, consisting of universal screening with OGTT and measurement of vitamin D status, is supported by The Norwegian Directorate of Health and collaborative partners in the city of Oslo (Stovner, Grorud and Bjerke administrative districts).

5 Results

5.1 Characteristics of the women

Of the 1018 participants, valid data necessary to estimate the prevalence of GDM between 24 and 34 weeks of gestation existed for 966 women (95%). Sixty-four percent were from an ethnic minority group, with the largest groups being composed of South Asians (24%) and Middle Easterners (16%). The study population, representing 73 different countries of birth, is categorized into seven ethnic groups and displayed in figure 2. Countries making up the categories, along with the numbers in each, are presented in table 2. Norway, Pakistan and Sri Lanka are the countries that contribute with most participants, with 334, 153 and 59 women, respectively. The group “South America”, consisting of only 16 women, is presented and included in the descriptive results, but will not be given emphasis or included in further regression analysis due to small sample size.

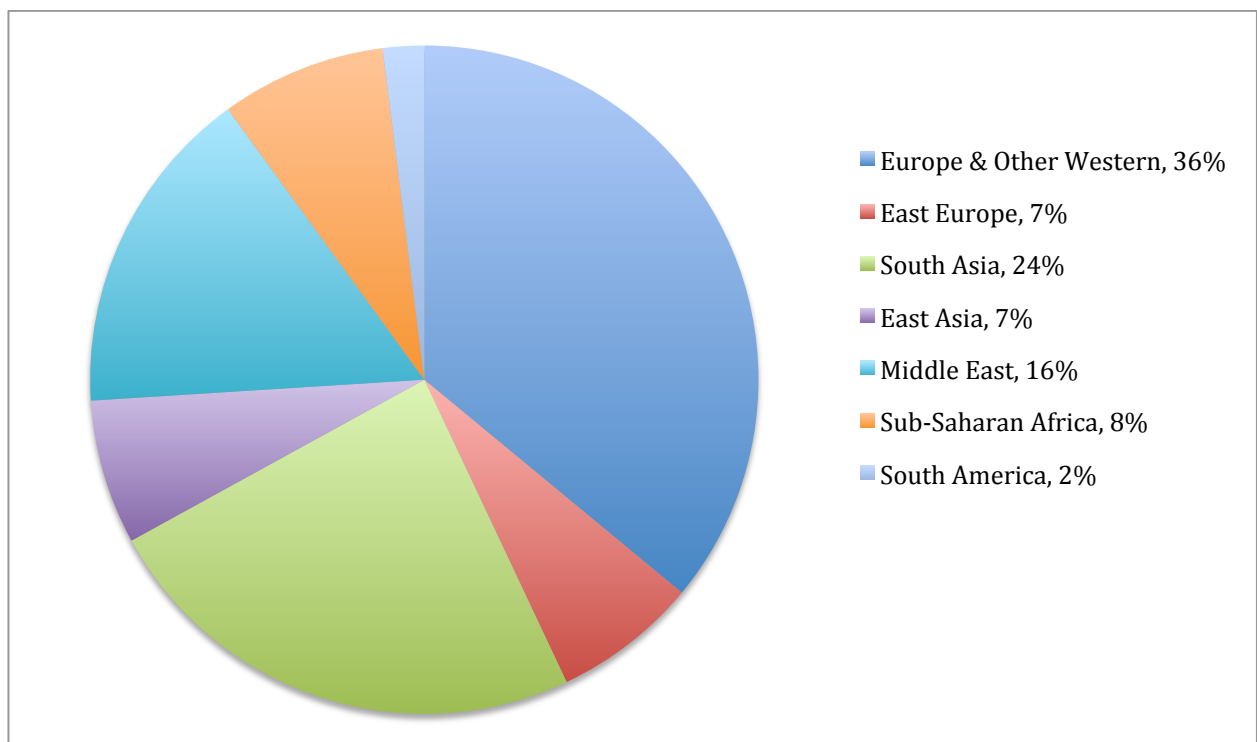


Figure 2: Pie chart showing the total cohort stratified into 7 ethnic groups with percentages (%).

Table 2 Ethnic origin of the study cohort, n=966. If less than 5 women have origin from a specific country, they are included in the group 'other'.

	N	%
Total	966	100
Europe & other Western	352	36
Norway	334	95
Sweden/Denmark/Finland	10	3
Other Western Europe	9	2
East Europe	69	7
Poland	19	28
Bosnia	10	15
Kosovo	6	9
Litauen	6	7
Makedonia	6	9
Romania	5	7
Other Eastern Europe	17	25
South Asia	232	24
Pakistan	153	66
Sri Lanka	59	25
India/Bangladesh	20	9
East Asia	65	7
Philippines	27	41
Vietnam	22	34
Thailand	11	17
Other East Asia	5	8
Middle East	153	16
Turkey	34	22
Afghanistan	28	18
Morocco	27	18
Iraq	26	17
Iran	15	10
Palestine	5	3
Other Middle East	19	11
Sub-Saharan Africa	78	8
Somalia	29	37
Ethiopia	18	23
Eritrea	8	10
Ghana	5	6
Other Sub-S. Africa	18	24
South America	17	2
Other South and Central America	17	100

Table 3 presents the baseline characteristics of the study population stratified into ethnic groups. The mean (S.D) maternal age at time of OGTT was 30.4 years (4.7), and the BMI was 27.5 kg/m² (4.2). The women from Norway and South America were the oldest, and had lower parity, while the Sub-Saharan Africans had the highest proportion of multiparous women (34.2%). East Asian subjects had the lowest BMI and Middle Eastern women the highest. The group with the highest proportion of relatives with diabetes was South America, followed by Middle East and South Asia. The fasting glucose level was lowest among women from East Asia (4.3 mmol/l (0.4)) and highest in women from South Asia (4.7 mmol/l (0.6)). On oral glucose tolerance testing, the groups Sub-Saharan Africa and 'Norway and other Western' had the lowest 2-h glucose levels. Norway had the highest levels of vitamin D while the Middle Eastern women had the lowest levels. Statistical significant differences between the ethnic groups were found for all parameters, and groups differing significantly from 'Norway and other Western' are marked with a footnote in the table.

Table 3 Characteristics of the sample stratified into ethnic groups. Data are mean (S.D) and n (%) unless otherwise stated.

	N	Total n=966	Norway* n=362 (37)	E. Europe n=71 (7)	S. Asia n=238 (24)	E. Asia n=66 (7)	Mid. East n=158 (16)	S-S. Africa n=78 (8)	S. America n=18 (2)	P
Age (years)	966	30.4 (4.7)	31.3 (4.5)	29.8 (4.8)	29.6 (4.6)** ¹	31.0 (5.1)	29.8 (4.9)**	29.5 (4.2)**	31.8 (5.0)	<0.001
Gestational age (weeks)	966	28.6 (1.5)	28.7 (1.5)	28.3 (1.4)	28.3 (1.6) ^{§§}	28.6 (1.3)	28.5 (1.4)	28.9 (1.8)	28.7 (1.3)	0.006
Parity, n (%)	871									<0.001
Nulliparous		396 (45.5)	181 (56.6)	28 (45.9)	75 (36.8)	27 (50)	55 (38.2)	21 (29.6)	9 (52.9)	
Uniparous		310 (35.6)	117 (36.6)	25 (41.0)	68 (33.3)	17 (31.5)	50 (34.7)	27 (38.0)	6 (35.3)	
Multiparous (≥ 2)		165 (18.9)	22 (6.9)	8 (13.1)	61 (29.9)	10 (18.5)	39 (27.1)	23 (34.2)	2 (11.8)	
BMI (kg/m²)	947	27.5 (4.2)	27.0 (3.9)	26.9 (3.7)	27.7 (4.0)	25.5 (2.5) [§]	28.5 (4.1)	27.5 (3.8)	27.6 (2.1)	0.001
BMI pre-pregnant (kg/m²)*	578	23.9 (3.8)	23.9 (3.9)	23.6 (3.8)	24.5 (4.2)	21.6 (2.0)**	24.5 (3.8)	24.2 (3.9)	24.3 (2.7)	<0.001
Height (cm)	963	163.7 (7.2)	168.2 (6.0)	166.9 (5.5)	159.9 (6.5)**	158.3 (5.6)**	161.7 (5.7)**	161.4 (6.2)**	160.4 (3.9)**	<0.001
Weight (kg)	954	73.9 (12.4)	77.7 (12.3)	76.2 (11.4)	70.8 (11.9)**	62.5 (7.5)**	74.2 (11.7)**	73.6 (11.9)	69.1 (8.1)**	<0.001
Body fat (percent)	947	37.4 (5.7)	36.9 (6.0)	36.7 (5.8)	38.5 (5.5)**	33.9 (4.4)**	37.5 (5.4)	40.1 (5.5)**	38.0 (4.6)	<0.001
Family with diabetes, n (%)	862	246 (29)	64 (20.2)	16 (25.0)	74 (35.9)	19 (35.2)	52 (38.0)	13 (19.1)	8 (50.0)	<0.001
Fasting glucose (mmol/l)	966	4.6 (0.6)	4.5 (0.5)	4.5 (0.5)	4.7 (0.6)**	4.3 (0.4)	4.6 (0.6)	4.6 (0.5)	4.6 (0.6)	<0.001
2-h glucose (mmol/l)	963	6.2 (1.4)	5.9 (1.3)	6.3 (1.2)	6.4 (1.5)**	6.4 (1.3)	6.4 (1.3)**	5.8 (1.3)	6.4 (1.2)	<0.001
Vitamin D (nmol/l)^a	954	73 (49)	88 (45)	81 (42)	61.0 (46)**	71 (57)**	58 (42)**	54 (56)**	65 (43)	<0.001
Earlier GDM, n (%)	445	34 (7.6)	4 (3.1)	4 (12.9)	14 (11.6)	5 (18.5)	4 (4.9)	2 (4.3)	1 (12.5)	0.012

* Data available from 578 women only

*Includes Norway & other Western countries

Differences are tested with ANOVA for continuous variables and chi-square for categorical variables.

**P<0.001, when compared with women from Norway & other Western, [§] P=0.001, when compared with women from Norway & other Western, ^{§§} p=0.006, when compared with women from Norway & other Western.

^a Median, IQR

A comparison between women who were included in the study (n=996) and those excluded (n=52) according to previously described criteria was also made (table 4). Among the women who participated and those who were excluded, the mean age and BMI was 30.4 years (4.7) and 27.5 kg/m² (4.1) and 29.5 years (4.6) and 26.3 kg/m² (4.5), respectively. Baseline characteristics did not differ significantly between those included and excluded, except for gestational week at OGTT, as expected.

Table 4 Baseline characteristics of the study cohort and excluded subjects. Data are mean (SD) or n (%).

	Study sample		Excluded		P*
	n=966		n=52		
	N		N		
Age (years)	966	30.4 (4.7)	51	29.5 (4.6)	0.187
Gestational age (weeks)	966	28.61 (1.5)	48	26.87 (6.2)	<0.001
Parity, n (%)	871		40		0.370
Nullip.		396 (45.5)		15 (37.5)	
Unip.		310 (35.6)		14 (35.0)	
Multip (>2)		165 (18.9)		11 (27.5)	
Ethnic origin, n (%)	966		51		0.192
Norway & Other W.		352 (36.5)		14 (27.5)	
Non-Western		614 (63.6)		37 (72.5)	
Family with diabetes, n (%)	862	246 (29)	35	12 (33)	0.536
BMI (kg/m ²)	947	27.5 (4.1)	44	26.3 (4.5)	0.058
Pre-pregnant weight (kg/m ²)	578	64.9 (11.7)	22	62 (16.1)	0.288
Fasting glucose (mmol/l)	966	4.65 (0.6)	48	4.69 (0.6)	0.668
Vitamin D (nmol/l)	954	76.1 (36.9)	50	66.9 (36.1)	0.084
City district, n (%)	966		52		0.101
Stovner		356 (36.9)		26 (50.0)	
Grorud		370 (38.3)		13 (25.0)	
Bjerke		240 (24.8)		13 (25.0)	

* p values from t-test and chi-square.

5.2 Prevalence of GDM

The number of women diagnosed as having GDM according to the WHO criteria was 132, giving a crude prevalence rate of 13.7 (95 CI: 11.5-15.8). The prevalence rates in the largest ethnic groups were 8.2% (95 CI: 5.3-11.0) in Western Europe, 20.3% (95 CI: 14.8-25.1) in South Asia and 19.0% (95 CI: 12.7-25.2) in Middle East (figure 3). The women from Sub-Saharan Africa had the lowest prevalence at 7.7% (95 CI: 1.7-13.6). When each ethnic group was compared with the group 'Norway & other Western', statistical significant differences in the prevalence were found for South Asia ($p<0.001$) and Middle East ($p=0.001$), while East Asia was borderline significant ($p=0.051$).

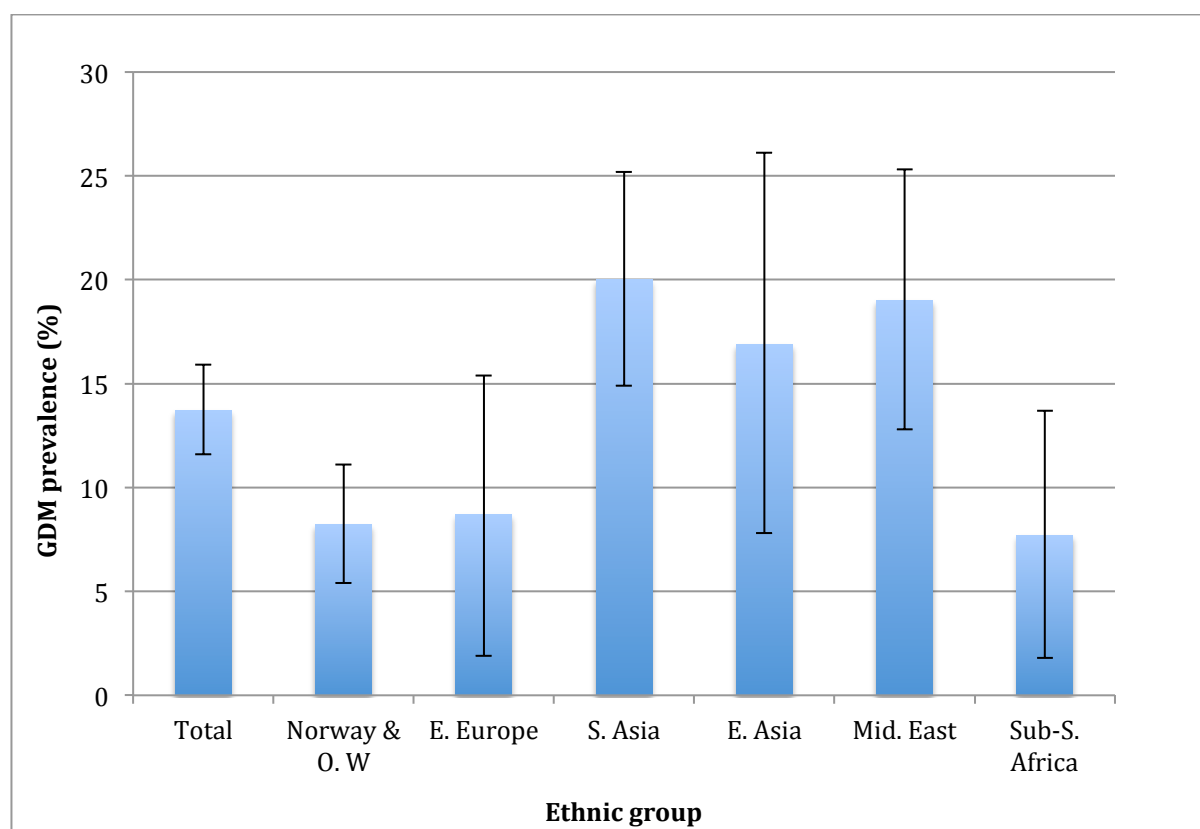


Figure 3: Crude GDM-prevalence, with 95% CI, according to the WHO-criteria, presented for the total cohort and 6 ethnic groups (South America not included due to small sample size).

5.2.1 Comparison with prevalence rates from STORK-Groruddalen study

In STORK Groruddalen (Jenum et al., 2012) the study sample consisted 759 women with had valid data in gestational week 28. The number of women diagnosed with GDM was 99, giving a crude prevalence rate of 13.0% with the WHO-criteria. Despite finding a similar total prevalence for the STORK cohort and the women in this study, the rates found for some of the ethnic groups are slightly different in the two (figure 4). However, overlapping confidence intervals indicate that the findings from this study do not differ from STORK. The Western European had a prevalence of 11% in the latter, compared to 8% found in this study. Contrary, the South Asian women have prevalence of 20.3% in this study compared to 14.8% in STORK. The East Asian and Middle Eastern have slightly higher prevalence rates in this study as well, while the Eastern European had a twice as high prevalence at 17.0% in STORK, compared to 8.5% found in this study. Moreover, when comparing the proportions in pairs of groups, none of the prevalence estimates were statistically significant different from one another. The results for the women from Sub-Saharan Africa and South America have not been compared, as these groups were merged into one in STORK, and are presented separately in the current study.

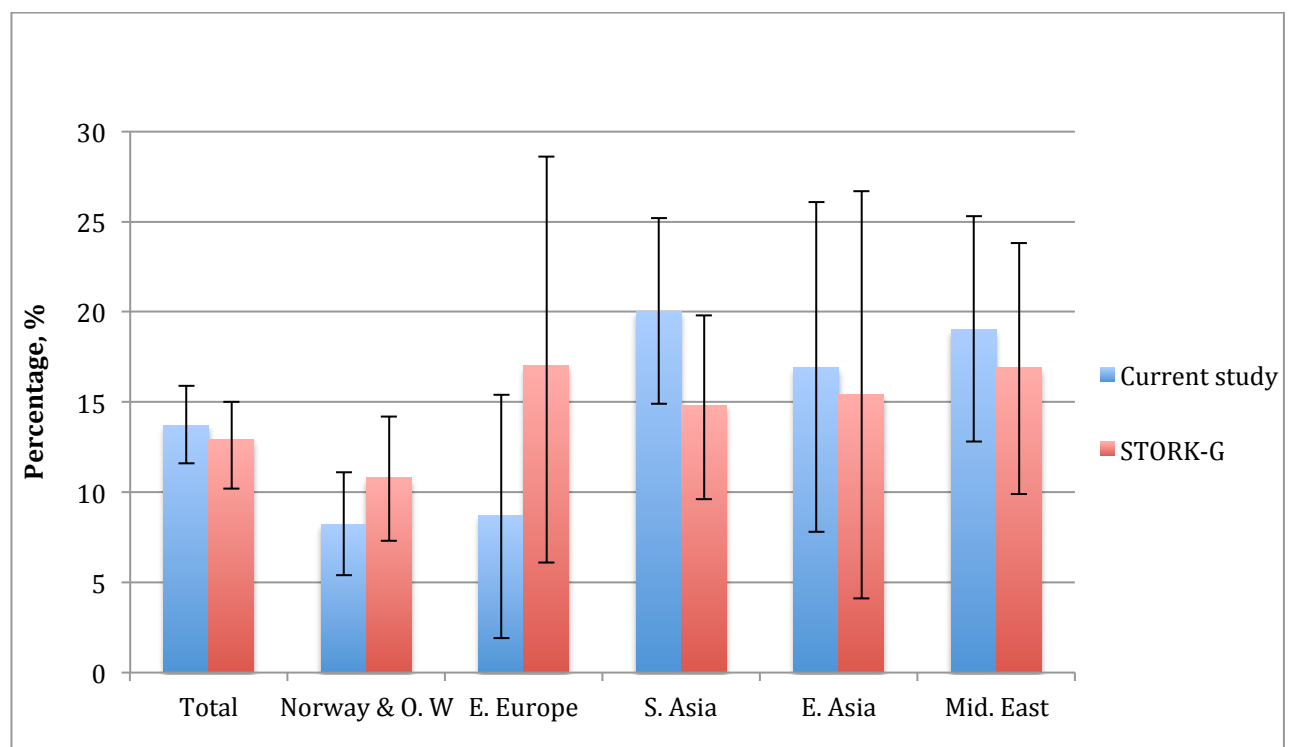


Figure 4: GDM-prevalence with 95% CI for the STORK Groruddalen study cohort and the current study sample, according to the WHO-criteria. Sub-Saharan Africa and South America are not presented due to different categories in STORK G.

5.3 Associations with GDM

5.3.1 Differences between the GDM and non-GDM group

The mean maternal BMI was significantly higher in women with GDM compared to women with normal glucose levels (table 5). Significant differences were also found when comparing ethnicity ($p<0.001$) and family history of diabetes ($p<0.001$). Body fat percentage ($p=0.002$), height ($p<0.001$) and vitamin D levels ($p=0.035$) were different between the non-diabetic group and the women who developed GDM as well. Age, parity, BMI pre-pregnancy and gestational age were not significantly different between the two groups.

Table 5 Characteristics of the GDM and non-GDM group. Values are expressed as mean (S.D) and n (%).

	Non-GDM n=833 (86.3)	GDM n=132 (13.7)	P⁺
Age (years)	30.4 (4.7)	30.4 (4.6)	0.996
Gestational age (weeks)	28.6 (1.43)	28.4 (2.14)	0.094
Ethnicity, n (%)			<0.001
Norway & Western	323 (39)	29 (21)	
East Europe	62 (7)	6 (5)	
South Asia	185 (22)	47 (36)	
East Asia	54 (6)	11 (8)	
Middle East	124 (15)	29 (22)	
Sub Saharan Africa	72 (8)	6 (5)	
South America	13 (2)	4 (3)	
Parity, n (%)			0.192
Nulliparous	342 (46)	53 (44)	
Uniparous	272 (36)	38 (31)	
Multiparous (>2)	135 (18)	30 (25)	
BMI (kg/m²)	27.4 (4.1)	28.3 (4.1)	0.014
BMI pre-pregnancy (kg/m²)*	23.9 (3.8)	24.4 (3.9)	0.232
Weight (kg)	73.9 (12.5)	73.7 (11.3)	0.861
Body Height (cm)	164.1 (7.3)	161.2 (6.5)	<0.001
Body Fat, (percentage)	37.2 (5.7)	38.9 (5.5)	0.002
Family history of diabetes, n (%)	190 (26)	56 (48)	<0.001
Vitamin D (nmol/l)	77.1 (37.4)	69.6 (33.0)	0.035

* Data available from 578 women only

⁺P values for the difference between the groups, tested with t-test and Pearson chi-square.

Figure 5 displays the prevalence of GDM calculated within three BMI classes, as defined by WHO: (1) normal: BMI <24.9 kg/m²; (2) overweight: BMI between 25 and 29.9 kg/m²; and (3) obese: BMI >30 kg/m², further stratified by ethnic group. For two of the groups, the prevalence of GDM rises with increasing category of BMI; however, this is not the case for women of Middle Eastern origin, indicating that the association varies markedly by ethnic group. Further, a linear trend was only observed for the South Asians (p=0.041), for which the prevalence more than doubled from the normal class (15.9%) to the obese class (31.0%).

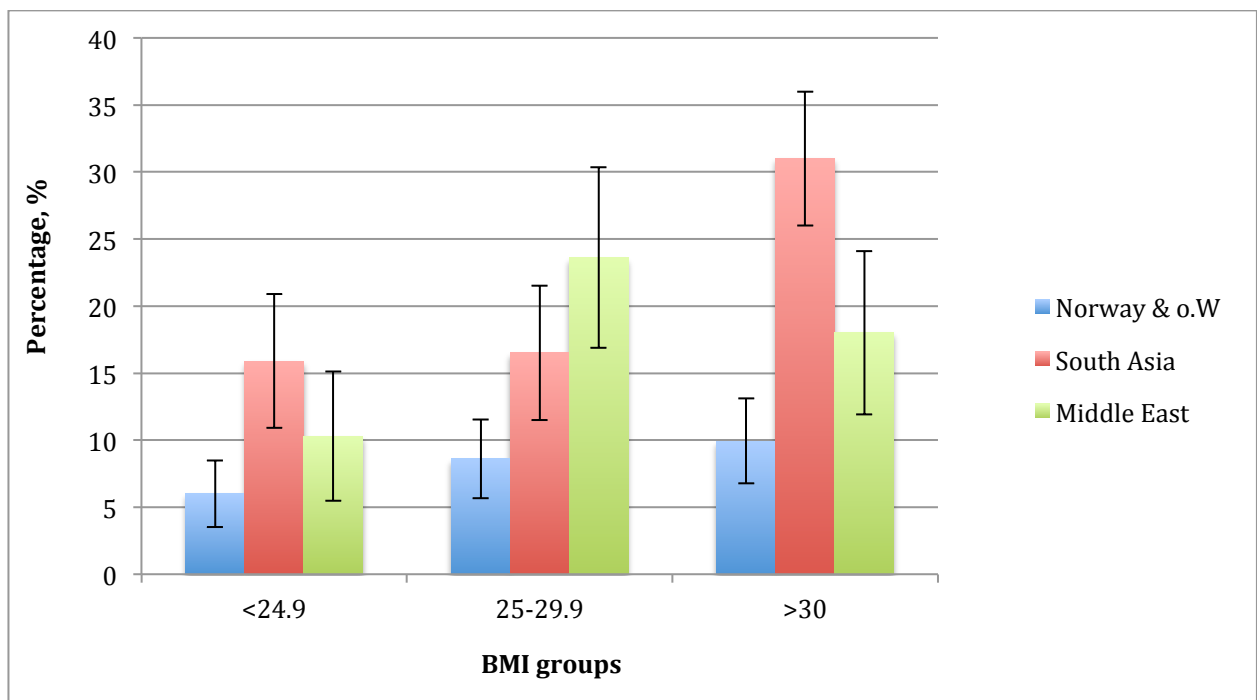


Figure 5: The prevalence rates of GDM with 95-CI according to classes of maternal body mass index (kg/m²), shown for three ethnic groups. Statistical differences tested with Person chi-square.

At a BMI of >30 kg/m², the prevalence of GDM was almost two times higher among Middle Eastern, and more than three times higher among South Asian women (18.0% and 31.0, respectively) compared with Norwegians (9.9%), a statistically significant difference (p=0.005). The ethnic groups differed significantly also at BMI 25-29.9 kg/m² (p=0.008), but not at <24.9 kg/m² (p=0.108).

Similar associations were not found between maternal age and GDM, nor were any strong trends observed (figure 6). The age categories were as follows: (1) 26.9 years; (2) 27-32.9 years; and (3) >30 years. The Western women had the highest prevalence of GDM in the

youngest age group, while the Middle Eastern had the highest rates in the oldest age group. For the South Asian women, the highest prevalence of GMD was found for the category 27-32.9 years. The three groups differed significantly from each other in both the latter age group ($p=0.001$) as well as in the highest age group ($p=0.013$).

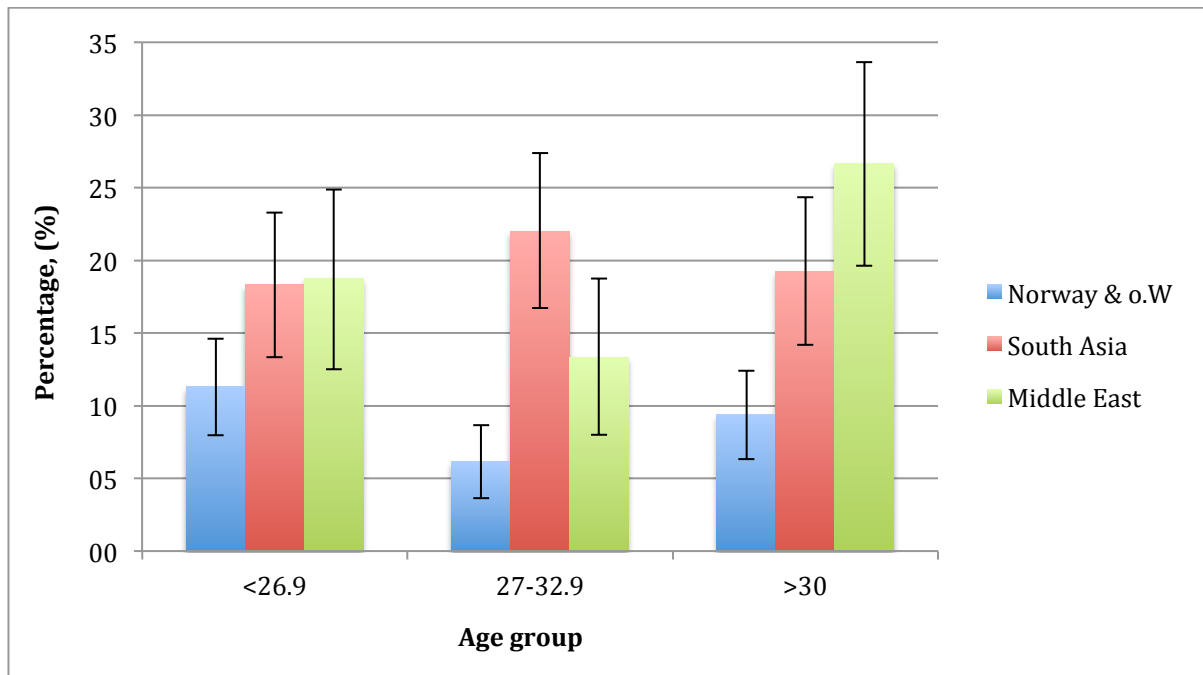


Figure 6 The prevalence rates of GDM with 95-CI in the study population according to age-groups, shown for three ethnic groups. Statistical differences tested with Person chi-square.

5.3.2 Effect of ethnicity on GDM

Logistic regression analyses were performed to assess the association of a number of factors on the development of GDM. The first column in table 6 presents univariate analysis for the variables. For GDM, ethnic origin from South Asia (OR: 2.66, CI: 1.54-4.59) and Middle East (OR: 2.42, CI: 1.34-4.37) was an independent factor, when adjusted only for age and parity (model A). After further adjustments for BMI and first-degree relatives with diabetes (model B), the observed associations were still present between these ethnic groups and the risk of GDM.

In the final model (model C) parity and BMI were removed and replaced with body fat percent, height and gestational age at OGTT. As shown in the table, four of the independent variables made an independent statistically significant contribution to the fully adjusted

model (ethnicity, family history of diabetes, height and body fat percentage). Having a background from South Asia and first-degree relatives with diabetes were the strongest factors of GDM, both recording an OR of 2.18. This indicates that women from South Asia and Middle East are more than 2 times likely to develop GDM when compared to the reference category Norway and other Western, controlling for all other factors in the model. Likewise, having first-degree relatives with diabetes increases the likelihood of developing GDM more than 2 times. The model as a whole explained 11.7% (Nagelkerke R squared) of the variance in GDM status.

Figure 6 Multiple logistic regression models, showing the impact of ethnic origin on the categorical outcome of GDM after adjusting for covariates.

	Univariate		Model A		Model B		Model C	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	1.00 (0.96-1.04)	0.996	0.99 (0.94-1.04)	0.867	0.99 (0.94-1.04)	0.802	1.00 (0.96-1.05)	0.699
Ethnicity								
Norway & Western (ref.)	1		1		1		1	
East Europe	1.06 (0.42-2.66)	0.900	0.72 (0.24-2.15)	0.563	0.87 (0.28-2.68)	0.814	1.28 (0.49-3.36)	0.606
South Asia	2.83 (1.72-4.65)	<0.001	2.66 (1.54-4.59)	<0.001	2.85 (1.56-5.20)	0.001	2.18 (1.17-4.04)	0.013
East Asia	2.26 (1.07-4.81)	0.033	2.04 (0.90-4.61)	0.087	1.91 (0.74-4.91)	0.176	1.50 (0.56-3.95)	0.411
Middle East	2.60 (1.49-4.53)	0.001	2.42 (1.34-4.37)	0.003	2.26 (1.17-4.35)	0.014	2.07 (1.07-4.00)	0.030
Sub Saharan Africa	0.98 (0.37-2.31)	0.873	0.75 (0.27-2.08)	0.589	0.98 (0.34-2.82)	0.987	0.76 (0.27-2.14)	0.604
Parrrity								
Nulliparous (ref.)	1		1		1			
Uniparous	0.90 (0.57-1.41)	0.658	0.89 (0.54-1.44)	0.635	0.92 (0.55-1.55)	0.766		
Multiparous	1.46 (0.88-2.34)	0.146	1.14 (0.63-2.06)	0.645	1.25 (0.66-2.36)	0.481		
BMI (kg/m²)	1.05 (1.01-1.09)	0.053			1.03 (0.98-1.08)	0.165		
First-degree relatives with diabetes	2.68 (1.80-3.99)	<0.001			2.39 (1.54-3.72)	<0.001	2.18 (1.43-3.34)	<0.001
Height (cm)	0.94 (0.91-0.97)	<0.001					0.96 (0.93-0.99)	0.045
Gestational week	0.99 (0.99-1.00)	0.095					1.00 (0.99-1.00)	0.886
Body fat (%)	1.05 (1.01-1.08)	0.003					1.05 (1.01-1.09)	0.006
Vitamin D (nmol/l)	0.99 (0.98-0.99)	0.035						
Pre-pregnant BMI (kg/m²)	0.99 (0.97-1.01)	0.472						
Weight (kg)	0.99 (0.98-1.01)	0.861						
Nagelkerke R²				0.056			0.110	0.117

6 Discussion

A discussion of the methodological considerations and the main findings in this study will be presented in this chapter.

6.1 Methodological considerations

When interpreting the results of a study, strengths and weaknesses of the methodology applied should be taken into account. This section aims to highlight, among other issues, possible effects of bias, the ethical aspect and the question of generalizability.

6.1.1 Study design

This study applies a cross-sectional design assessing the prevalence of GDM at a specific point in time, e.g. the scheduled check-up where universal screening for GDM is performed. Applying a cross-sectional design has several limitations as well as some advantages. A major advantage of this study is that the design makes it possible to collect information about many potential risk factors, and provides a broad base of knowledge about subjects who have/do not have the outcome of interest (Frigessi et al., 2006). In addition, such surveys provide useful information regarding the health status, behavior or trends of a population or specific group, which is essential for assessing the health needs and planning for appropriate health services (Yu & Tse, 2012). To this end, the current study may contribute to our knowledge about GDM, more precisely its frequency and potential risk factors, which is highly crucial information with importance for future development and improvement of antenatal care in Oslo.

Cross-sectional studies are sometimes carried out to investigate associations between risk factors and the outcome of interest (Levin, 2006), although establishing cause-and-effect relationship between exposure and outcome is impossible (Frigessi et al., 2006). Because such studies are carried out at one time point, they do not give any indication of the sequence of events – whether exposure occurred before, after or during the onset of the disease outcome (Levin, 2006). In this study, a number of risk factors are found to be associated to the development of GDM. However, Information from before the actual pregnancy or from early gestation is lacking, making it difficult to infer causality between GDM and pre-pregnancy factors. However, some exposures registered in this study, such as ethnicity, parity

and diabetes in family, are background factors independent of time; they are demographics characterizing the women. With BMI, on the other hand, which is shown to be associated with GDM (Chu et al., 2007), we cannot assume whether the high BMI existed before pregnancy, or is a result of the pregnancy. Worth to mention is also the fact that data on potential risk factors (age, parity, BMI etc.) were obtained before performing the OGTT. Neither the midwife nor the women knew the results of the blood tests at the point of data collection, implying that answers given are likely to be less influenced by the outcome of the screening.

6.1.2 Bias and measurement error

Errors are inevitable in almost any epidemiological studies, even in the best conducted research designs. When interpreting findings it is essential to consider carefully how much the observed association between an exposure and an outcome may have been affected by errors in the design, conduct and analysis (dos Santos, 1999). Bias refers to any trend in the collection, analysis or interpretation of data that can lead to results that are systematically different from the truth (Mosdol & Brunner, 2005). In this chapter, three broad categories of bias, selection bias, information bias and confounding will be discussed, in addition to measurement error.

6.1.2.1 Selection bias

Selection bias occurs when there is a difference between the characteristics of the people selected for the study and those who would be theoretically eligible but did not participate, and may result from using improper procedures for selection of subjects from the target population (dos Santos, 1999). In this study, two sources of potential selection bias should be considered. Estimating the number of theoretically eligible subjects e.g. all pregnant women living in the district, may be rather difficult as it requires a close monitoring of babies being born in the period and also taking in consideration women moving in and out of the area. Our best estimate indicate that about 70-80% of women living in these districts attended the CHC at least once during their pregnancy. Individuals with chronic diseases or medical conditions necessitating intensive specialist follow-up are unlikely to attend the CHC, and some also choose to visit private obstetricians. The first source of error would therefore be the exclusion from the study sample of those not attending the CHC's. In that case, the prevalence of GDM might have been different among those included than among the population from which they

came from (Mosdol & Brunner, 2005). Our findings suggesting 13.7% GDM prevalence might be an underestimate if some women with high risk choose to see GP's etc. instead of attending the CHC.

Of those attending the CHC, a number of women were not offered the OGTT. The reasons for this are presented in the flowchart (figure 1); however, in contrast to STORK Groruddalen, we do not know exactly how many women should be classified into each category of not being invited. For instance, the number of women who had already been tested at their GP's or arrived too late was not registered. In STORK, attendance at the CHC too late in pregnancy was the main reason for not being invited, constituting 81.7% of those not invited (Jenum et al, 2010). Practical challenges at the CHC also influenced the total number of invited women. As around 1-2 midwives and only one laboratory personnel are responsible for screening at each CHC, women arriving during periods of sick leave or holidays are most likely not offered OGTT. Our best estimate, suggesting 77% participation of all invited, could therefore be subject to some uncertainty. Nevertheless, a participation rate of 77% is higher than in most studies today and is considered satisfying according to Johannessen et al. (2010), as it is above 50%.

Furthermore, when some women (5%) were excluded from the analyses according to previously defined criteria, the scope of bias must be reassessed. Exclusion was done mainly on the basis of gestational week at point of screening and invalid OGTT data. However, upon analysis, baseline characteristics of subjects included and excluded did not differ significantly, except for gestational age, as expected (table 4).

Gestational age at point of OGTT is commonly recommended between 24-28 weeks'. However, some women attend the CHC's later or earlier than this. These women should ideally be excluded so that only women arriving in a set time between 24-28 weeks' would constitute the study sample. In the current study, a less restrictive, but still medically acceptable criterion for inclusion of women attending was applied, e.g. between 24-32 weeks'. Also, a few women with the GDM diagnosis were included despite arriving before these set criteria (at 20 weeks') due to their risk profile. These women would probably have GDM at 28 weeks' as well, and were included for this reason. Gestational week is always adjusted for in the multivariate statistical analyses.

The women attending the CHC's for antenatal care have not been informed about the current study, as it was decided on later. Consequently, selection bias associated with recruitment is not an issue. If this group of women was invited to participate in this study, but only a subset was willing to take part, selection bias could be expected. This is because participants who volunteer to take part in such a study are likely to be more educated and health conscious (Mosdol & Brunner, 2005), or perhaps aware of their risk of GDM. Avoiding recruitment to this specific study probably has resulted in a larger number of women included, especially in some ethnic groups, compared to the STORK Groruddalen study (Jenum et al, 2012). Requesting written consent after obtaining data may introduce selection bias, as those willing to participate not necessarily represent the population of interest. This challenge is further explored in chapter 6.1.4 under ethical considerations.

6.1.2.2 Information bias

Information bias results from differences in the assessment of the exposure, outcome or other relevant variables, and occurs in the data collection stage of studies (Frigessi et al., 2006; Mosdol & Brunner, 2005). In this study, potential errors in measurement may be introduced by the observer or the instruments being used to perform the measurements.

Interviewer-administrated questionnaire

The questionnaires are filled out together with midwives. Obtaining the information that the questionnaires were designed to seek requires that the women understand the questions being posed. Secondly it requires that the language in which the conversation takes place is fully understood by responders. Professional translators were used when needed in the STORK Groruddalen study (Jenum et al, 2010), and also in the current study. Nonetheless, there is a possibility that some questions might have been misunderstood or were not completely understood even though interpreters were in daily use. The use of interviewer-administrated questionnaires offers several advantages that could reduce such issues. For one, questions and responses can be clarified (WHO, 2008). The midwives have the opportunity to explain complex or difficult questions with a simpler wording and may ensure that everything is completely understood. Moreover, such questionnaires are very useful if women visiting the CHC's are less literate or illiterate, which there are cases of in Groruddalen. An additional strength of such questionnaires administered by an interviewer is fewer "blanks", as the person posing the questions can make sure no fields are left unanswered (ibid.) However, this

advantage was not fully reflected in this study, as many variables were observed to have a high number of missing (table 3).

Although questions are understood fully, conceptual matters, cultural relevance and the associations of words and phrases impact how an individual perceives it (Hunt & Bhopal, 2004). This is of particular relevance for the question of first-degree relatives with diabetes. What is defined as a first-degree relative may differ across ethnic and cultural group. Some groups, for instance, South Asians could be defining cousins/uncles/aunts and extended family as first-degree relatives, while other, such as ethnic Norwegians, could be including only their close family, e.g. parents and siblings. A common understanding of this question is essential and requires that the interviewer explain whom to include in the term “first-degree relatives”. The Middle Eastern and South Asian group in this study have reported higher portions of relatives with diabetes (38% and 36%, respectively) compared to Norwegians (20%). One possible explanation for this could be that these groups have included extended family as well, which may affect the findings. On the other hand, there is also a possibility that these portions are even higher than reported considering that numerous individuals have unknown or undiagnosed diabetes (Jenum et al., 2005).

Anthropometry and blood tests

The major limitation of anthropometry is the extent to which measurement error can influence the interpretation of results. Achieving high levels of precision and accuracy is important and individuals performing the measurements should be given good training (Bates et al., 2005). During STORK, the study staff members were certified after extensive education, training courses, and on-site supervision (Jenum et al, 2010). Although not supervised in the current study, experienced midwives are responsible for measuring height, weight and drawing blood. Also, if one person makes all the anthropometric assessments in a study, there is only within-observer measurement error to consider. However, the current study covers three CHC'S in different districts areas (Stovner, Grorud and Bjerke), requiring several anthropometrists over a period of nearly two year. This may add potential measurement errors (Bates et al, 2005). Intra- and inter-rater variability was assessed every sixth month in STORK, but this was not done in the current study conducted in a non-research setting.

Furthermore, some measurement errors may have occurred when screening for GDM with the OGTT. As noted previously, a large number of women experienced nausea, resulting in vomiting. Although those who vomited before one hour passed were excluded, approximately 8 women vomiting after one hour have been included. This could affect the 2-h plasma values obtained. Furthermore, at times the CHC staff experienced some difficulties when drawing blood in respect to finding the vein. As a result, it was decided to draw blood test in the finger instead. Such cases were not excluded and a lack of consistency in the measurement of glucose may consequently have occurred.

6.1.2.3 Confounding bias

A confounder is any factor that can cause or prevent the outcome of interest and at the same time is associated with the exposure in a way that it distorts the observed relationship between the two factors of interest (Mosdol & Brunner, 2005). An important question to consider in this study is whether the associations between GDM and observed risk factors can be due to a third variable associated to both the risk and outcome. Age is a common confounder in many studies since the risk of diseases usually increases with age. This risk factor could be confounding with both BMI and parity. In addition, the multifactorial cause of GDM may be determined by many conditions that are not known or were not measured in this study. An example is diet and physical activity, both of which could be potential cofounders of BMI. These risk factors were examined in STORK but information on them was not collected in the current study. Confounders can be controlled for in statistical models (Mosdol & Brunner, 2005), however it is not always clear whether a factor is confounding or not.

6.1.3 Internal and external validity

Internal validity is the degree to which the results of a study are correct for the sample of patients being studied. It is determined by how well the design, data collection, and analyses are carried out, and threatened by all of the biases discussed above (Fletcher, Fletcher, & Fletcher, 2012). The absence of such biases (selection, information and confounding bias) is essential for the external validity (Frigessi et al., 2006). It refers to the degree to which the results of an observation hold true in other settings. Another term for external validity is generalizability (Fletcher et al., 2012), expressing the validity of assuming that women in this study are similar to other women.

As previously discussed, both in this study and in STORK (Jenum et al., 2010), the estimates based on data monitoring the activity at the CHC suggest that the majority of pregnant women living in the city districts attend the CHC for antenatal care. However, not all women prefer this option, and some probably choose to see their general practitioner or have all their follow-ups in specialist hospital care. For instance, women with known pre-gestational diabetes or those suffering from various conditions with potential impact on the pregnancy may need intensive follow-up by specialist already from the first trimester. These women are probably less likely to attend CHC's for additional antenatal care. Thus, the study population could be considered representative only of healthy pregnant women in Groruddalen, as only these attend the CHC's. There could also be cases of women visiting private obstetricians instead, however, there is little reason to believe that many would choose this option (Sletner, 2014).

The city districts in Groruddalen have a large proportion of the non-Western population in Norway (Statistics Norway, 2014) and it can be assumed that women attending the CHC's are representative for healthy women in reproductive age from the main ethnic groups living in the area (Jenum et al., 2010). Ethnic minority women are often underrepresented in most of the research projects, partly due to language and cultural barriers (Rooney et al., 2011). When participation is restricted to individuals with the ability to speak, read and understand Norwegian, several groups of particular interest for the study objectives may be lost. Moreover, inclusion of these groups was of great importance in this study, as the aim was to explore ethnic differences in the prevalence and risk factor of GDM. The CHC-setting has facilitated the inclusion of such hard to-reach groups in this study by collecting the data routinely and as a part of the standard care delivered to all women.

6.1.4 Ethical considerations

Research without consent is controversial, and some ethicists argue that it is almost never appropriate (Conaboy, 2013). In this study, access to personal health information without written consent, was given by the REC after presenting satisfying justification. The argumentation consisted of the three following conditions under which it is reasonable to conduct research involving access to personally identifiable data: (1) the proposed research is socially and publicly valuable; (2) obtaining consent would be practically impossible after data collection, or would likely bias the research; and (3) to minimize the intrusion of

privacy, strict safeguards for access are implemented and confidentially ensured (Miller, 2008). In this chapter, an elaboration of this justification will follow.

Observational research drawn from medical records, such as the current study, does not involve experimentation with human subject or any interaction between researchers and human subjects. Nothing is being done to or with the persons whose records are accessed, and there is no interference with their freedom or the course of their lives, especially since confidentiality of the data is protected (Miller, 2008). However, privacy is invaded by that the right to control access to private information, especially sensitive medical information obtained in the course of standard medical care, is taken away.

To avoid such invasion of privacy, efforts could be made to contact the individuals involved prior to accessing their data for analysis. The women could be informed about the study and its purpose, and given the opportunity to opt-out of the research. However, seeking consent after data collection is quite challenging, especially in this particular study population. For one, participants have background from around 73 different countries, resulting in the need for consent forms in a large number of languages. Translating the consent forms and all relevant information in all these languages would be extremely time and resource consuming. Moreover, a significant number of women are illiterate making it rather impossible to explain the purpose of the study in a letter.

Secondly, locating human subjects in order to obtain consent poses a well-known barrier, especially in large samples (Black, 2003). Many women move out of the area or change contact information. Others return to their countries of origin, or visit for longer or shorter periods. Individuals not responding are not assumed to be passively refusing consent, but rather being difficult to reach. When efforts are made to obtain informed consent, selection biases can be introduced into the data, as those who consent are not necessarily representative of the population of relevant patients (Miller, 2008). It is therefore likely that seeking consent after, rather than prior, to study enrolment may compromise the study's scientific validity.

Demonstration of an important public purpose for the research is of particular high value when taking use of private data without consent. Medical records can be a public resource for generating evidence relating to improving health care and population health (Miller, 2008).

However, it requires finding a balance between individual privacy and public goods, but by no means sacrificing the rights of individuals for the welfare of society. In this study, the potential for public benefit is thought to be high and the risk of harm to individuals low. As far as we know, only three CHC's in Groruddalen have improved their antenatal care by offering screening for GDM to all pregnant women. This organizational change has been both resource-consuming and increased the workload for midwives in the respective city districts. It is therefore essential that such changes are evaluated and their value assessed. If the findings of the current study suggest high prevalence of GDM, as reported in STORK (Jenum et al., 2012), screening for GDM should continue to be prioritized in these CHC's, and should perhaps be offered in other parts of Oslo with high minority rates as well.

Lastly, because these records contain sensitive personal information, mandating strict standards for protecting the private data from unwarranted use that can be harmful to individuals is ethically necessary (Miller, 2008). De-identifying of data as soon as possible after registering in Epidata is one of the steps taken to ensure privacy protections. In addition, when presenting the results, countries with less than 5 women are included in a group 'other'.

Harms and benefits for the women

For women undergoing an OGTT, benefits apply in terms of identification of possible high glucose values. Information about the consequences of GDM for both mother and offspring was given, along with lifestyle advice aimed at preventing or treating the condition, mainly consisting of changes in diet and physical activity. The benefits of the screening are greater for those diagnosed with GDM, as the women likely wouldn't be identified otherwise, or perhaps later in the pregnancy. Moreover, life style advice given may prevent future type 2-diabetes in women and their children (Knowler et al., 2002), if followed post pregnancy as well.

It has been suggested that screening for GDM can cause unnecessary anxiety for pregnant women (Hjelm, Berntorp, Frid, Aberg, & Apelqvist, 2008; National Institute for Health and Clinical Excellence, 2008). The OGTT is ideally offered between gestational weeks 24 to 28, at a point where most women no longer have nausea and vomiting associated with the first months of pregnancy. Nevertheless, a number of women experience hyperemesis when drinking the sweet glucose mix, and some end up vomiting as well. As previously noted, around 24 women (of which 16 were excluded) experienced vomiting in this study, making it

difficult to complete the test. However, a French study discovered that, overall, 97% of those screened judged the test to be acceptable, even though approximately half experienced nausea during testing and just under half found the test stressful (Gayet-Ageron et al., 2008).

Other than these discomforts, no harms are associated with the OGTT. This study does not influence the women's outcome and therefore confer no risk and no benefit to participants.

6.1.5 Statistical methods

When performing statistical analyses there is a possibility of reaching the wrong conclusion, as our results can be subject to two types of errors. The size of the sample is a large determinant of reporting false-negative findings, also called type II error e.g. believing that the groups do not differ when in fact they do (Pallant, 2010). A large study sample is one of the strengths in this study, as larger samples are expected to give more reliable results and have the advantage of greater statistical power (Nayak, 2010). Although the probability of type II error is reduced by including 966 women, some of the groups compared are quite small, in particular South America (table 3). This ethnic group was included in the ANOVA analysis of variance, but not in other analyses for this reason. For the comparison of prevalence with rates from STORK, two of the groups, Sub-Saharan Africa and South-America, could not be compared due to these groups being merged into one in STORK. The same categorizing could have been made in the current study, making the comparison of these groups possible. However, this was recognized at a late point and therefore not done.

Further, the risk for the second type of error is high in this study and should be considered carefully when interpreting the findings. Type I error refers to the possibility of finding a difference between groups when one does not actually exist (Pallant, 2010). For instance, one might conclude that there is a difference between the seven ethnic groups included for several variables, when in fact, there isn't. Moreover, with large samples even small differences between groups may become statistically significant. Thus, one should be aware that such differences not always have any practical or theoretical significance (Pallant, 2010). In this study, the differences found in, for instance, age, BMI or glucose levels, between groups are not necessarily big or meaningful.

To reduce the probability of type I error and minimize the possibility that the variation observed is due to chance, the level of statistical significance could have been reduced to 1%. However, as many of the differences observed are highly significant ($p < 0.001$) similar results would probably be obtained with a more stringent alpha level as well. In addition, post-hoc comparisons are designed to guard against the possibility of an increased type I error due to the large number of different comparisons being made (Pallant, 2010).

For the risk factors identified with the multiple regression analysis, large increases in the OR's are observed, for instance a doubled risk of GDM for certain ethnic origins. This indicates that the differences are large and important. Formal tests of interactions were not performed before performing the regression analysis, which should ideally be done as an essential step and prerequisite for these types of analyses; however, simple descriptive analyses did not indicate interaction.

In this study, several variables such as age, BMI, body fat etc. are presented as continuous variables in the descriptive statistics. Similarly, they were not categorized for the regression analyses. These variables could have been recoded into categorical forms, so that the distribution of data could be clearer. Height in particular could be interesting to explore, as there are obvious differences in the classes tall and short, according to ethnic origin.

6.2 Discussion of the main findings

To our knowledge, this is the first study in Europe in a multiethnic population of healthy pregnant women, where the prevalence rates and risk factors for gestational mellitus diabetes are measured by universal screening offered as part of the routine care, outside a research setting. In the following chapters, the results from this study will be discussed and viewed in light of previous research in the field.

6.2.1 Prevalence

In this multiethnic population of women undergoing universal screening with OGTT, overall 13.7% were found to have GDM, and the prevalence varied by ethnic group. South Asia was the group with highest prevalence, followed closely by women from Middle East. Significant differences in the prevalence rates were also found for these groups when compared with Norwegian women. Our results are consistent with other studies reporting high prevalence of GDM and T2DM in immigrants from these ethnic groups (Hedderson et al., 2012; Jiwani et al., 2012). In contrast, African women and ethnic Norwegians had the lowest prevalence. Similarly, Hedderson et al. (2010) found the lowest prevalence of GDM among white (non-Hispanic) women and blacks when comparing 11 race-ethnicity groups in the US.

As previously noted, comparing prevalence rates from other studies is difficult as there is no international consensus regarding the screening procedure for GDM (Buckley et al., 2012; Jiwani et al., 2012; Vandorsten et al., 2013). In Norway, the prevalence has not been assessed in a population-based cross sectional study before STORK, and representative data regarding rates of GDM in the total population are not available. The Medical Birth Registry of Norway from 2007 reported a total incidence of 1.3%, a number ten times lower compared with findings from this study (Norwegian Institute of Public Health, 2007). Other studies from comparable populations found lower rates as well (Galtier, 2010), while a Finnish registry data study reported a GDM-prevalence of 10-11% (Lamberg et al, 2012). Observed differences in the prevalence rates could be attributed to trends in age and BMI of the study population (Flack, Ross, Ho, & McElduff, 2010), and numbers are probably hampered by unsystematic screening and underreporting. In addition, the current study includes women with ethnic minority background, which in most cases increases the total prevalence found.

Comparing the results with findings from the STORK Groruddalen study is more relevant as the methods and criteria (WHO 1999) applied are identical. However, some differences in demographics, e.g. BMI, age and other relevant parameters, for the two study populations may exist. Although not significant, observed differences in GDM prevalence rates for some ethnic groups in the current study compared to STORK could be explained by the variation in countries of origin for several ethnic groups. For instance, fewer women from Somalia participated in this study compared to STORK (37% and 65%, respectively), and a larger proportion of individuals are included from Poland (28% and 16%, respectively) (Mørkrid, 2013).

6.2.2 Associations of ethnicity and other risk factors

When controlled for maternal age and parity, ethnic minority background from South Asia and Middle East was significantly associated with GDM. These associations persisted after further adjustments for BMI and first-degree relatives with diabetes. Multiparity is suggested as a risk factor but findings are inconsistent as the relationship between parity and GDM is closely linked to two potential confounding factors, age and BMI (Dode & Dos Santos, 2009; Galtier, 2010). As women from ethnic minority groups were more likely to be multiparous compared to Norway and other Westerns, parity was included in the regression analysis in this study. However, this factor was non-significant in both model A and B, and parity was therefore not included in model C.

BMI was also removed in the final model and replaced by body fat, as significant associations with GDM were not apparent. However, when assessing the prevalence of GDM according to BMI classes, a trend was observed indicating increasing prevalence rates with increasing BMI (figure 5). This was not observed in the Middle Eastern group for which the highest prevalence was found in the overweight class (BMI 25-29.9 kg/m²). Also, for each BMI class, the ethnic minority groups were more susceptible for GDM compared with the group Norway & other western.

Furthermore, even at the lowest BMI cut point (<24.9 kg/m²), all groups showed high rates of GDM, suggesting that the disorder not only affect overweight and obese subjects, but also women with normal weight. The prevalence was especially high (15.9%) in the lowest BMI category for the South Asians in particular. This is in line with other studies reporting that

women from South Asia develop GDM at younger ages and lower BMI compared with other groups (Makgoba, Savvidou, & Steer, 2012). Hedderson et al. (2012) also found that the risk for GDM is high even at relatively low BMI cut-offs in Asian women.

The reasons for a higher risk of GDM found at a lower BMI for Asians have been discussed but are still unclear. Ethnic differences in the percentage total body fat per BMI unit are reported in many studies (Deurenberg, Deurenberg-Yap, & Guricci, 2002; A. Misra & Khurana, 2011; Yajnik & Ganpule-Rao, 2010) and it has been concluded that Asians generally have a higher percentage body fat and more visceral adipose tissue compared with other ethnic groups (Lear, Humphries, Kohli, & Birmingham, 2007; Wulan, Westerterp, & Plasqui, 2010). This has led to a growing debate about the definition of overweight and obesity in Asian population, and the WHO proposed a different cut-off for these BMI categories (WHO Expert Consultation, 2004). Instead of classifying overweight at 25 kg/m^2 , the new cut-off suggests 23.0 kg/m^2 for Asian populations. These cut-off values, which have not been applied in this study, would most likely have revealed other findings.

Advanced maternal age is another well-recognized risk factor for GDM (Dode & Santos, 2009). In this study, however, increasing age did not necessarily lead to higher rates of GDM (figure 6). This was further confirmed in the regression analysis, where age was not significantly associated with GDM. When comparing the Middle Eastern, South Asian and Western women, the latter ethnic group showed the highest prevalence in the lowest age category of <26.9 years. The rates for this age category were high also in the other groups (18.8 and 18.3, respectively), implying that a number of women develop GDM in a young age. It is however, not clear whether these young individuals with GDM are obese or overweight, as additional analyses adjusting for both BMI and age at the same time were not performed.

The national guidelines in Norway recommend selective screening of GDM for women belonging in a high-risk group, where two of the criteria are age >38 years and BMI $>30 \text{ kg/m}^2$ (Directorate for Health and Social Affairs, 2009). The findings from this study indicate that screening of women based on these risk factors could lead to a number of women not being identified, as many have GDM even in the absence of obesity and older age. Thus, the potential for missing a significant proportion of GDM cases following such recommendations for selective testing is high. In addition, these guidelines suggest considering the woman's

ethnic origin when determining her risk for GDM and the need for screening. Contrary to age and BMI, our findings support the importance of this risk factor, as ethnic origin from both South Asia and Middle East were found to be associated with GDM.

Height and gestational week at inclusion were also added to model C. In contrast to the STORK study, information on socioeconomic factors, such as educational level or employment, was not registered in the current study. Body height, however, may be used as a proxy for socioeconomic determinants related to stunting, and gives essential information on the mother's nutritional status or living conditions during fetal and/or early life (Jenum et al., 2005; Ogonowski & Miazgowski, 2010). For this purpose, height was included in the final model. An inverse association between height and GDM was found in this study, suggesting, in line with others (Galtier, 2010; Jenum et al., 2012; Kew et al., 2010; Ogonowski & Miazgowski, 2010) that low adult height is associated with GDM.

A number of studies have suggested ethnic origin from South Asia and Middle East as a risk factor for GDM (Hedderson et al., 2010) but findings are inconsistent (Dode & Dos Santos, 2009). Although still significant, the increased OR for women from South Asia and Middle East were reduced in the final model after additional adjustment for height and body fat. Similar findings were reported in the STORK Groruddalen study (Jenum et al., 2012) where the OR decreased for both of these groups and were no longer significant after adding early life SEP (height and education) to the model. Addressing this issue, Link & McKinlay (2009) showed that socioeconomic status is more important in determining diabetes rather than race/ethnicity, reinforcing findings from a number of other studies (Connolly, Unwin, Sherriff, Bilous, & Kelly, 2000; Cunningham et al., 2008; Rabi et al., 2006).

Family history of diabetes, a well-documented risk factor for GDM (Galtier et al, 2010; Dode & Dos Santos, 2009), remained highly significant even in the fully adjusted regression model. As vitamin D status showed statistically significant OR for GDM in the univariate analysis, this factor was added to a fourth model. The estimates were unchanged in this model, and vitamin D status was not statistically significant when controlled for the other covariates (data not shown).

In STORK (Jenum et al, 2012) other factors than those found in the current study were significant in the fully adjusted model, one being maternal age, which was not significant

even in the unadjusted analyses in this study. Parity was also significant contradictory to our findings. However, it should be noted that parity was categorized differently in the regression analysis in STORK, as parous (≥ 1), compared to three categories in this study. Additionally, the model contained pre-pregnancy BMI as compared to the current study where maternal BMI or percentage body fat has been used. Although shown in the univariate analyses, pre-pregnancy BMI was not included in the models as data were lacking for one city district. The main difference is, however, that ethnic origin was not found to have an impact on GDM when controlled for other covariates in STORK. While ethnic origin from South Asia and Middle East showed increased OR in the current study, these OR would most likely be reduced when adding the variable education to the model, as was done in STORK.

The R^2 for the fully adjusted model, including both potentially modifiable risk factors and the non-modifiable risk factors, found that they together explain only 11.7 percent of the variation in GDM status. The large proportion (88.3%) of unexplained variation indicates that other factors associated with GDM remain to be identified or should have been included in the models. Factors that could have an impact are physical activity, diet and socioeconomic factors such as educational level, employment and the woman's proficiency in Norwegian. Similarly, information on how long the women had been living in Norway and on the degree of acculturation could also have been recorded, both of which may influence the risk of GDM (Hedderson et al, 2010).

6.3 Strengths & limitations

A major strength of this study is the CHC setting in which universal screening is offered as an integrated part of the routinely antenatal consultations. This allows for a high inclusion rate when assessing the prevalence of GDM. Most women accepted to perform the OGTT and appreciated the opportunity to check for this condition that could affect their pregnancy and offspring. As all patients have been given this possibility, selection bias is likely to be reduced. In STORK Groruddalen, several ethnic groups were small, and the numbers have been increased in most groups in this study.

This study also had some limitations. We lacked data on several potential confounding factors, including physical activity and diet. The observational design of this study makes it impossible to conclude that GDM is causally related to the risk factors observed; however,

such a relationship is plausible. Finally, It should be recognized that though larger than in the Groruddalen study, some ethnic groups were still relatively small. Because of limited numbers, we were unable to examine associations separately among subgroups of the sample (for instance for Somali women). The broad categorization of some ethnic groups will in addition fail to address differences that may exist within the same group, e.g. the Middle Eastern group, comprising a wide range of countries. The anthropometry as well as metabolic profile of women from, for example, Afghanistan may differ from that of women with Turkish origin.

6.4 Implications for public health

The results from this study show high prevalence of GDM, and the rates are higher among some ethnic groups compared to Norwegians. With the increasing prevalence of obesity, one can expect further rise in the rates of GDM in the coming years, especially in conjunction with a multiethnic population and advancing maternal age in Norway. This has important implications for public health policy. As maternal glucose increased, there is a higher expected rate of caesarean section, preeclampsia, large for gestational age babies and neonatal hypoglycemia (Hapo Study Cooperative Research Group et al., 2008). This will in turn have significant impacts on clinical workload and require additional resource allocation (Sweeting, Rudland, & Ross, 2013). Additionally, GDM requires care during pregnancy as well as continued care in the long term and follow up.

As women have repeated contact with the health system during pregnancy, this period provides health professionals with a unique opportunity to provide education and to encourage healthy dietary habits and increased physical activity (Metzger et al., 2007). The CHC's in Groruddalen and midwives play a crucial role in early identification of GDM and pre-existing diabetes by offering universal screening as part of the routine care. Furthermore, as GDM is considered a risk factor for T2DM (Landon & Gabbe, 2011; Pedersen, 1971), its diagnosis provides an invaluable opportunity to highlight women at risk of future diabetes. This enables general practitioners in addition to midwives, to engage in targeted monitoring and early life style intervention in the post-partum period as well (Sweeting et al., 2013). Given the strong evidence showing that lifestyle changes can prevent or delay the progression of T2DM in women with previous GDM (Knowler et al., 2002), this intervention opportunity should be embraced.

Moreover, it is of particular importance to identify women with impaired glucose tolerance and GDM at an early stage, so that appropriate treatment can be initiated to prevent adverse outcomes. Undiagnosed or poorly managed diabetes or hyperglycemia during pregnancy is associated with a higher risk of maternal and perinatal morbidity and mortality as well as poor pregnancy outcomes (World Diabetes Foundation [WDF] & Global Alliance for Women's Health [GAWH], 2008). However, by screening patients merely on the basis of risk factors, one may not be able to detect all women with GDM, affecting the number of women who are not given the diagnosis and hence do not proceed to treatment. Several studies have confirmed that risk factor-based screening fails to identify some women with GDM (Anderberg, Kallen, Berntorp, Frid, & Aberg, 2007; Baliutaviciene, Petrenko, & Zalinkevicius, 2002; Minsart, Lescrainier, & Vokaer, 2009). This may have major consequences for public health, as allowing hyperglycemia in pregnancy may maintain a “vicious cycle” by increasing the risk of obesity, impaired glucose tolerance and diabetes in later generations (Castorino & Jovanovic, 2011).

An accurate diagnosis of pregnant women with GDM, on the other hand, offers the possibility to decrease such conditions in future generations. There is also potential for intergenerational prevention of several other chronic diseases such as arterial hypertension, cardiovascular disease and stroke. Thus, one high-quality intervention related to maternal health service as universal screening for GDM, makes it possible to achieve several objectives with far reaching health and economic benefits (WDF & GAWH, 2008). Referring to the growing crisis of obesity and T2DM in both young and adult populations – a rapidly increasing portion of the global disease burden - Castorino and Jovanovic (2011) emphasized that failing to identify women with GDM and hence allowing hyperglycemia would be “adding fuel to the fire”. Yet, current guidelines (The Directorate for Health and Social Affairs, 2009) recommend selective screening, shown to score poorly in predicting GDM, perhaps due to economic and health system workload reasons. There is, however, not an agreement on which screening approach is optimal, as there is evidence pointing in favor of both selective and universal screening in the scientific literature. For instance, a large Danish study of over 5000 women reported that screening based on risk factors was as effective as universal screening (Jensen et al., 2003).

With universal screening as part of the routine care one can expect an increase in the number of women diagnosed with GDM. The most obvious consequence of these additional

diagnoses is related to the health care cost and such financial implications clearly need serious consideration. In addition, the “medicalization” of pregnancy is also of concern, as a diagnosis of GDM may include labeling or treating women with mild gestational glucose intolerance with increased interventions and more intensive surveillance during pregnancy (Moses, 2010).

As GDM is increasing with the increasing burden of obesity in women, its prevention depends on the prevention of obesity among young women of reproductive age. Prevention strategies should therefore focus on education on healthy diets and harms of obesity. Also, as mounting evidence supports a relation between growth and development during fetal and early life and health in later years, investment in the health and education of young women regarding their responsibilities during pregnancy and parenthood is of fundamental importance (Gluckman et al., 2008). Hence, a life-course perspective, in addition to a lifestyle perspective, should be promoted in any approach to health care. Moreover, awareness-raising among public, patients and providers about the risk of GDM as well as advocacy and training, are needed to prevent or reduce GDM in the population. Also, the results from many studies suggest that socioeconomic factors matter, perhaps more than ethnic origin per se. Interventions to prevent the onset of diabetes should therefore be focused even more on groups with low socioeconomic status.

Future research

Public health initiatives to address diabetes in pregnancy, such as universal screening for GDM, can be integrated into existing routines for antenatal care, as demonstrated by the CHC's in Groruddalen. Such programs may be initiated more widely, for instance in other parts of Oslo, either in CHC's or other antenatal services. However, economic implications related to the implementation of universal screening need to be taken into account. Future studies should therefore focus on the cost effectiveness and benefit of detecting and treating GDM, which has been questioned by those who are skeptical to universal screening in routine care. The national guidelines recommend selective screening as per today, and a change in these guidelines in favor of universal screening for all pregnant women along with its implementation will most likely result in increased health system workload.

Prior to suggesting such major structural changes in the antenatal care in Norway, there is a need to estimate resources needed, in addition to advantages and limitations of this initiative

for the three city districts in Groruddalen where this had been integrated in the routine. Cost effectiveness analyses of the economic impact of implementing universal screening could give several answers. This may help consider whether universal screening of GDM and its management is cost-effective and should be added to the standard antenatal care package.

7 Conclusion

The overall prevalence of GDM found in a multiethnic population in Groruddalen (Stovner, Grorud and Bjerke city districts) was 13.7%, and large differences were observed for the main ethnic groups. The highest prevalence rates were found for the women from South Asia and Middle East, while the lowest were found for women from Norway and other Western countries. This study further indicates that ethnic origin from South Asia and Middle East, first-degree relatives with diabetes, lower height and higher percentage body fat are associated with increased GDM risk. Such risk factors could help identify women with higher risk of GDM; however our findings suggest that women without some of these risk factors (older and overweight/obese) may develop GDM as well.

The prevalence rates found in this study where OGTT was offered as part of the routine care are in line with the prevalence reported in the STORK Groruddalen research program. Our findings seem to justify universal screening as an integrated part of the antenatal care in this area with large proportions of ethnic minorities. Nevertheless, the benefit of detecting and treating GDM through standard routine care should be assessed in future studies.

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Appendix 1

STORK GRORUDDALEN - SPØRRESKJEMA GRAVID



Navn:		Fødselsdato:
Termin etter siste mens:		Termin etter ultralyd:
Tidligere svangerskap:		Fasttelefon: Mobiltelefon:
Antall:	Lev.født:	Stilling / yrke:
Fødeland:	Første besøk: (dato):	Etnisk opprinnelse hvis kvinnene eller hennes mor er født utenfor Europa):
Høyde:	Vekt: før graviditet	Hvis ikke fra Skandinavia:
	Første besøk: (dato):	Botid i Norge (antall år):
		Tolkebehov: Ja Nei Språk:
Tanita: legg ved strimmel og kopi av strimmel ↓	BMI	Vekt: Besøk uke 28 ± 2 (dato):

SPØRSMÅL OM DIABETES:

Hatt svangerskapsdiabetes tidligere: Ja Nei
Diabetes i mors familie: Ja Nei

Fastende BLODPRØVER I uke 28 (± 2) :

Dato: Glukoseverdi 0 timer (mmol/l) →	HemoCue (tatt lokalt):	sykehusvar:
Dato: Glukoseverdi 2 timer (mmol/l) →	HemoCue (tatt lokalt):	sykehusvar:
Svangerskapsdiabetes	Ja: Nei:	
Dato:	Vitamin D verdi:	

OPPFØLGING ved SVANGERSKAPSDIABETES og avvikende vitamin D verdier

Gitt skriftlig info (STORK brosjyre) på foretrukket språk:	Ja	Nei
Henvist sykehus hvis fastende ≥ 7 mmol/l eller 2 timers verdi ≥ 9 mmol/l	Ja	Nei
Underrettet fastlege (STORK- brev med ansvarlig jordmors underskrift)	Ja	Nei
Henvist fastlege (STORK-brev med ansvarlig jordmors underskrift)		
Hvis 2 timers verdi ≥ 7,8 – 8,9 mmol/l	Ja	Nei
Hvis lavt D-vitamin _Sendt brev	Ja	Nei